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Clinical Research

Impact of Serial B-Type Natriuretic Peptide Changes for Predicting Outcome in Asymptomatic Patients With Aortic Stenosis

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ABSTRACT

Background: The aim of this study was to determine the impact on the outcome of serial B-type natriuretic peptide (BNP) changes during follow-up in asymptomatic patients with ≥ moderate aortic stenosis (AS) and preserved left ventricular ejection fraction.

Methods: We prospectively screened 69 patients who underwent comprehensive transthoracic echocardiography, BNP level measurement at baseline and after every 6 or 12 months. Annualized BNP changes were calculated as the difference between the last and baseline BNP measurements divided by the duration of follow-up. The primary endpoint was the occurrence of symptoms, aortic valve replacement, or cardiovascular death.

Results: During a follow-up of 30 ± 19 months, 43 patients experienced a cardiac event. These patients were significantly older (73 ± 9

RÉSUMÉ

Introduction : Cette étude avait pour but de déterminer l'effet des variations du taux de peptide natriurétique de type B (BNP) mesuré par dosage répété durant le suivi des patients asymptomatiques présentant une sténose aortique modérée ou grave et une fraction d'éjection ventriculaire gauche préservée.

Méthodes : Nous avons sélectionné de manière prospective 69 patients ayant subi une échocardiographie transthoracique minutieuse de même qu'un dosage initial du BNP, répété tous les 6 ou 12 mois par la suite. La variation annualisée du taux de BNP a été calculée comme étant la différence entre le dernier dosage et le dosage initial, laquelle était ensuite divisée par la durée du suivi. Le paramètre principal était la survenue de symptômes, d'un remplacement valvulaire aortique ou du décès d'origine cardiovasculaire.

Aortic stenosis (AS) is the most common valvular heart disease.[1] Current indications of aortic valve replacement are mainly based on the presence of symptoms and/or left ventricular (LV) dysfunction.[2,3] Risk stratification of asymptomatic patients with AS and preserved LV ejection fraction (LVEF) is challenging, and controversy persists regarding the best timing for surgery. First of all, severity assessment is performed by Doppler echocardiography, an operator-dependent technique that requires expertise. Early recognition of symptoms can be difficult and subjective, especially in the sedentary elderly population, leading to concerns in regard to the "wait for symptoms" strategy.[4,5] Some argue to avoid unnecessary operative-related mortality by the "wait for symptoms" strategy; others claim that asymptomatic patients could be operated early.[6,7] Therefore, the use of reproducible predictors of outcome, less dependent on human factor error, is crucial to improve the management of patients with AS and precisely determine which patients could have the best benefit from an "early surgery" strategy.

B-type natriuretic peptide (BNP) is a reproducible biomarker predominantly secreted by ventricular cardiac myocytes in response to increased wall stress preceding the occurrence of symptoms.[8] Previous studies already showed that single measurement of a BNP level correlates with AS severity and their harmful consequences on diastolic function, functional status,

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vs 65 ± 16 years; $P = 0.010$), had more often dyslipidemia (79% vs 42%; $P = 0.038$), more severe AS (peak velocity: 3.9 ± 0.6 vs 3.5 ± 0.6 m/s; $P = 0.002$), larger indexed left atrial area (10.2 ± 2.5 vs 8.7 ± 1.9 cm^2/m^2; $P = 0.006$), and a higher increase in annualized BNP (+90 ± 155 vs +7 ± 49 pg/mL/y; $P = 0.010$). Patients with higher annualized BNP changes (> 20 pg/mL/y) had a significantly lower cardiac event-free survival (1 year: 63 ± 8% vs 97 ± 3%; 3 years: 31 ± 8% vs 68 ± 8%; $P < 0.001$). Using the multivariate Cox proportional hazards model, higher annualized BNP changes were significantly associated with increased risk of cardiac events (hazard ratio: 2.73, 95% confidence interval: 1.27-5.86; $P = 0.010$) after adjustment for age, dyslipidemia, and echocardiographic parameters.

Conclusions: In asymptomatic patients with AS and preserved left ventricular ejection fraction, the use of serial BNP changes may help to anticipate development of class I indication for aortic valve replacement.

Résultats : Durant un suivi de 30 ± 19 mois, 43 patients ont eu un événement cardiaque. Ces patients étaient significativement plus âgés (73 ± 9 ans vs 65 ± 16 ans; $P = 0,010$), étaient plus nombreux à présenter une dyslipidémie (79 % vs 42 %; $P = 0,038$) ou une sténose aortique grave (vélocité maximale de 3,9 ± 0,6 m/s vs 3,5 ± 0,6 m/s; $P = 0,002$), avaient un volume auriculaire gauche indexé plus grand (10,2 ± 2,5 cm^2/m^2 vs 8,7 ± 1,9 cm^2/m^2; $P = 0,006$) et une augmentation du taux annualisé de BNP plus marquée (+90 ± 155 pg/ml/an vs +7 ± 49 pg/ml/an; $P = 0,010$) par comparaison aux autres sujets de l'étude. La survie sans événement cardiaque était en outre significativement inférieure (1 an : 63 ± 8 % vs 97 ± 3 %; 3 ans : 31 ± 8 % vs 68 ± 8 %; $P < 0,001$) chez les patients présentant des variations annualisées du BNP plus élevées (> 20 pg/ml/an). L'utilisation du modèle de risques proportionnels de Cox a révélé une association significative entre les variations annualisées du BNP plus élevées et un risque accru d'événement cardiaque (rapport de risques de 2,73; intervalle de confiance à 95 % : 1,27 à 5,86; $P = 0,010$), après l'ajustement tenant compte de l'âge, de la dyslipidémie et des paramètres échocardiographiques.

Conclusions : Chez les patients asymptomatiques présentant une sténose aortique et une fraction d'éjection ventriculaire gauche préservée, le dosage répété du taux de BNP en vue d'en déceler les variations pourrait permettre d'établir une indication de classe I pour le remplacement valvulaire aortique.

and symptomatic deterioration.[9-11] Moreover, recent European Society of Cardiology guidelines have suggested BNP level measurement for risk stratification in asymptomatic AS.[2] Some authors have evaluated serial BNP measurements in patients with valvular heart disease demonstrating a better prediction of outcome compared with single measurements.[12,13] Accordingly, we previously published a related paper providing interesting insight into the relationship between the increase in serial BNP and the presence of LV systolic and diastolic dysfunction.[14] However, in AS, little is known about prediction of outcome using serial changes in BNP levels. The aim of the present study was to identify whether serial changes in BNP levels during the follow-up of asymptomatic patients with AS and preserved LVEF could predict outcome.

Methods

Study population

Consecutive asymptomatic patients with at least moderate AS (aortic valve area < 1.5 cm^2) and preserved LVEF (> 50%) referred for clinical evaluation and Doppler echocardiography to our heart valve clinic were prospectively screened. A careful history and exercise testing confirmed the asymptomatic status. Patients with concomitant > mild mitral valve disease or aortic regurgitation were excluded. Concomitantly, BNP level measurement was performed at baseline and repeated after at least 6 months of follow-up, and then, after every 6 or 12 months, in all 69 included patients. The institutional review boards approved the study and all patients gave written informed consent.

Echocardiographic measurements

Transthoracic Doppler echocardiographic examination was performed with a GE Vingmed VIVID 9 ultrasound system (Horton, Norway). The acquisitions were stored and subsequent off-line analyses were performed using a dedicated workstation (EchoPac, General Electric Healthcare, Little Chalfont, UK). The LV outflow tract area was multiplied by the LV outflow tract velocity time integral measured by pulsed-wave Doppler to calculate the LV stroke volume. The bi-apical Simpson disk method was applied to measure the LV end-diastolic and end-systolic volumes, and ejection fraction. Pulsed-wave Doppler at mitral inflow was used to measure peak E-wave and A-wave velocities and tissue Doppler imaging with pulsed-wave Doppler at the level of septal and lateral mitral annulus for e′ velocities. The E/e′ ratio was calculated using the average of septal and lateral mitral annulus e′ peak velocity. The LV global longitudinal myocardial deformation was evaluated from standard 2D images with adequate frame rate (≥ 60/s) by speckle tracking analysis. Manual tracing of the endocardial borders on an end-systolic frame was performed, and automatically tracking on subsequent frames was applied. Adequate tracking for each segment was verified and manually corrected, if necessary. The global longitudinal strain was the average of the segment strains from apical 4-, 2-, and 3-chamber views.[15] Peak and mean aortic gradient were calculated using the simplified Bernoulli equation with the aortic transvalvular maximal velocities obtained by continuous-wave Doppler, and the continuity equation was used to calculate the aortic valve area.[16] The left atrial (LA) area was obtained by planimetry in the apical 4-chamber view at end-systole. Systolic pulmonary artery pressure was derived from the tricuspid regurgitant maximal velocity using the modified Bernoulli equation and the addition of estimated right atrial pressure.

Serial BNP measurements

Venous blood samples were drawn at rest with chilled ethylenediaminetetraacetic acid tubes, centrifuged immediately

at 4000 rpm (4°C) for 15 minutes, and processed by an immunofluorescence assay (Biosite, Beckman Coulter, San Diego, CA). The assay detection was 1 pg/mL, and inter- and intra-assay variations were 5% and 4%, respectively. Annualized BNP changes were calculated as the BNP changes (difference between the last BNP measurement obtained during the follow-up and the baseline BNP measurement at inclusion) divided by the time between baseline measurement and last follow-up measurement:

$$\text{Annualized BNP changes (pg/mL/y)} = \frac{(\text{Last BNP at follow-up} - \text{Baseline BNP at inclusion})}{\text{Time of follow-up}}$$

Cardiac event-free survival

Patient follow-up was individualized and performed according to current guidelines, that is, every 6 or 12 months. Follow-up information was obtained after a complete medical chart review and discussions with the patients and/or general physicians. The follow-up was complete in 66 patients (96%). The primary endpoint was the occurrence of the first composite endpoint defined as the occurrence of symptoms, aortic valve replacement (indicated by symptoms or LV dysfunction according current class I indication),[2,3] or cardiovascular death.

Statistical analysis

Data were expressed as mean ± SD for continuous variables and comparisons obtained with Student's *t*-test. Percentages were utilized for categorical variables and group comparison obtained with the χ^2 test. Spearman's correlation coefficient was applied to analyze the relationship between annualized BNP changes and continuous parameters. To determine the independent predictors of annualized BNP changes, variables with a P value < 0.20 in univariate analysis were submitted to a stepwise backward multiple-regression analysis. To avoid colinearity among AS severity variables, we entered only peak aortic velocity in the multivariate model. The impact of annualized BNP changes on outcome was assessed according to median and tertiles. Probabilities of cardiac event-free survival were obtained by Kaplan-Meier estimates and compared with a two-sided log-rank test. Cox proportional hazards models were used both in univariable and multivariable analyses to identify the independent predictors of cardiac event-free survival. Gender and baseline BNP levels were forced into the first multivariable model regardless of the P value as they may influence annualized BNP changes.[9,17,18] Variables with a P value < 0.10 in univariable were incorporated into the second multivariable model. To avoid colinearity between parameters, statins, mean aortic pressure gradient, and indexed valve area were not included in the second model. Using the median of annualized BNP changes as a cutoff value, sensitivity and specificity for the prediction of the occurrence of events were determined with a receiver operating characteristic (ROC) curve. A P value ≤ 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Advanced Statistics 21.0.

Results

Determinants of annualized BNP changes

Among the 69 included patients, mean BNP at baseline was 96 ± 135 pg/mL (median: 62) and it significantly increased during the follow-up (last measurement: mean 180 ± 233 pg/mL [median 98]; $P < 0.001$). More than half of the patients (61%, n = 42) had more than 3 follow-up measurements, and the duration of follow-up between the baseline and the last measurement was 24 ± 17 months. The mean of annualized BNP changes was +59 ± 132 pg/mL/y (median: 20). Statistically significant correlations were found between annualized BNP changes and age ($r = 0.271$; $P = 0.024$), aortic severity parameters (peak aortic velocity: $r = 0.312$; $P = 0.009$), indexed LA area ($r = 0.293$; $P = 0.018$), and baseline BNP ($r = 0.275$; $P = 0.022$). There was a trend observed between the E/e′ ratio ($r = 0.235$; $P = 0.057$) and annualized BNP changes. There were no significant correlations between annualized BNP changes and LV mass ($P = 0.344$), volume (indexed end-diastolic: $P = 0.833$), ejection fraction ($P = 0.254$), and global longitudinal strain ($P = 0.188$). After adjustment for age, baseline BNP, global longitudinal strain, and E/e′ ratio, multivariable analysis identified the peak aortic velocity ($\beta = 56.7 \pm 16.9$; $P = 0.002$) and the indexed LA area ($\beta = 11.6 \pm 4.76$; $P = 0.018$) as independent determinants of annualized BNP changes during follow-up.

Impact of annualized BNP changes on cardiac event-free survival

During a global follow-up (baseline BNP measurement to the last follow-up) of 30 ± 19 months, 43 patients (62%) presented a cardiac event. The duration of follow-up between the last BNP measurement and the last follow-up was 6 ± 11 months. Aortic valve replacement was performed in 37 (54%) patients motivated by the occurrence of symptoms in 27 (39%) patients and by an abnormal exercise test showing symptoms clearly related to AS in 10 (14%) patients. Among the 6 (9%) remaining events, 4 (6%) were related to the development of patient symptoms but were treated medically because of prohibitive high surgical risk and 2 (3%) patients died from a cardiovascular cause. Patients with a cardiovascular event were significantly older, and had more often dyslipidemia, more severe AS, and a larger indexed LA area (Tables 1 and 2). In addition, they had higher BNP at follow-up and annualized BNP changes, but there was no difference according to BNP at baseline. Only those patients experiencing a cardiovascular event had a significant increase in BNP level from baseline to follow-up (Fig. 1).

Cardiac event-free survival was 81% ± 5% and 49% ± 6% at 1 and 3 years, respectively. According to the median of annualized BNP changes, patients with lower annualized BNP changes had a significantly higher cardiac event-free survival (1 year: 97% ± 3% vs 63% ± 8%; 3 years: 68% ± 8% vs 31% ± 8%; $P < 0.001$; Fig. 2). Similar results were found according to tertiles of annualized BNP changes: patients in tertile 3 had a significantly reduced 2-year event-free survival compared with tertile 1 (46 ± 11% vs 82 ± 8%; $P = 0.001$; Fig. 3). Using the multivariable Cox proportional hazard model, higher annualized BNP changes were independently associated with increased risk of cardiac events after adjustment for sex and baseline BNP; and age, dyslipidemia, and

Table 1. Comparison of demographic and clinical data according to adverse cardiac events

Variables	Whole cohort (n = 69)	No events (n = 26, 38%)	Events (n = 43, 62%)	*P* value
Demographic and clinical data				
Age (y)	70 ± 12	65 ± 16	73 ± 9	0.010
Male sex, n (%)	42 (61)	15 (58)	27 (63)	0.674
Body surface area (m^2)	1.8 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	0.379
Heart rate (bpm)	70 ± 11	70 ± 10	71 ± 12	0.735
Systolic arterial pressure (mm Hg)	146 ± 19	145 ± 20	147 ± 19	0.673
Baseline BNP, pg/mL (median)	96 ± 135 (62)	83 ± 128 (49)	104 ± 140 (67)	0.526
Risk factors				
Hypertension, n (%)	37 (54)	13 (50)	24 (56)	0.639
Diabetes mellitus, n (%)	14 (20)	7 (27)	7 (16)	0.309
Dyslipidemia, n (%)	49 (71)	15 (42)	34 (79)	0.038
Coronary artery disease, n (%)	14 (20)	3 (12)	11 (26)	0.146
Smoking, n (%)	20 (29)	6 (23)	14 (33)	0.367
Atrial fibrillation, n (%)	6 (9)	1 (4)	5 (12)	0.255
Medications				
β-Blockers, n (%)	38 (55)	15 (58)	23 (53)	0.813
ACE inhibitors, n (%)	18 (26)	7 (27)	11 (26)	0.947
AR antagonists, n (%)	8 (12)	2 (8)	6 (14)	0.412
Diuretics, n (%)	14 (20)	5 (19)	9 (21)	0.828
Statins, n (%)	41 (62)	12 (46)	29 (67)	0.061

ACE, angiotensin converting enzyme; AR, angiotensin receptor.

echocardiographic parameters, including peak aortic velocity and indexed LA area (Table 3). The only other factor besides annualized BNP changes identified as an independent predictor of cardiac events was the indexed LA area (hazard ratio [HR]: 1.15, $P = 0.05$). Similarly, tertile 3 of annualized BNP changes was independently associated with a significantly worse cardiac event-free survival (HR: 2.20, $P = 0.036$) as compared with tertile 1. The ROC curve analysis (AUC = 0.79) showed good sensitivity and specificity of annualized BNP changes > 20 pg/mL/y to predict the occurrence of events in the next 6 ± 11 months following the last BNP measurement: 71% and 77%, respectively (Fig. 4).

Discussion

The main findings of the present study, including asymptomatic patients with preserved LVEF and moderate-to-severe AS, are as follows: (1) patients with a cardiac event had significantly higher annualized BNP changes, despite similar baseline BNP, than those without a cardiac event during follow-up; and (2) patients with higher annualized BNP changes (> 20 pg/mL/y) multiplied by 2.73 their risk of cardiac events, even after adjustment for age, dyslipidemia, and echocardiographic parameters.

Pathophysiology of BNP release in AS

In AS, chronic pressure overload imposed on the LV leads to progressive LV hypertrophy, a compensatory mechanism aiming to maintain normal LV wall stress. However, at a later stage, when this compensatory mechanism is overridden, LV wall stress and filling pressure increase triggering BNP activation and release.[19] In symptomatic AS, BNP release has been shown to reflect the elevation in LV filling pressures.[20] In symptomatic or asymptomatic severe AS with structural impairment such as diastolic dysfunction, LA dilatation, LV hypertrophy, and fibrosis, elevated single BNP level measurement is a marker of already elevated LV filling pressures predicting poor short-term outcome.[9,10] However, in asymptomatic moderate-to-severe AS without significant structural changes, the baseline BNP level is potentially more dependent on the overall patients' picture (age, gender) rather than on the degree and consequences of AS.[18] This

Table 2. Comparison of echocardiographic data according to adverse cardiac events

Variables	Whole cohort (n = 69)	No events (n = 26, 38%)	Events (n = 43, 62%)	*P* value
AS severity				
Peak aortic velocity (m/s)	3.8 ± 0.7	3.5 ± 0.6	3.9 ± 0.6	0.002
Mean aortic pressure gradient (mm Hg)	37 ± 14	29 ± 9	42 ± 14	< 0.001
Indexed valve area (cm^2/m^2)	0.53 ± 0.13	0.58 ± 0.13	0.50 ± 0.12	0.019
LV geometry and function				
Indexed mass (g/m^2)	88 ± 26	85 ± 30	90 ± 23	0.472
Indexed end-diastolic volume (mL/m^2)	45 ± 12	45 ± 14	45 ± 12	0.999
Indexed end-systolic volume (mL/m^2)	15 ± 5	15 ± 5	14 ± 6	0.642
Indexed stroke volume (mL/m^2)	45 ± 10	44 ± 10	46 ± 9	0.559
LV ejection fraction (%)	67 ± 6	66 ± 7	69 ± 6	0.176
GLS (%)	−20 ± 3	−20 ± 3	−20 ± 3	0.848
E/e′ ratio	11 ± 4	10 ± 4	11 ± 4	0.630
Indexed left atrial area (cm^2/m^2)	9.6 ± 2.4	8.7 ± 1.9	10.2 ± 2.5	0.006
Systolic pulmonary arterial pressure (mm Hg)	36 ± 9	34 ± 7	37 ± 10	0.318

AS, aortic stenosis; BNP, B-type natriuretic peptide; GLS, global longitudinal strain; LV, left ventricular.

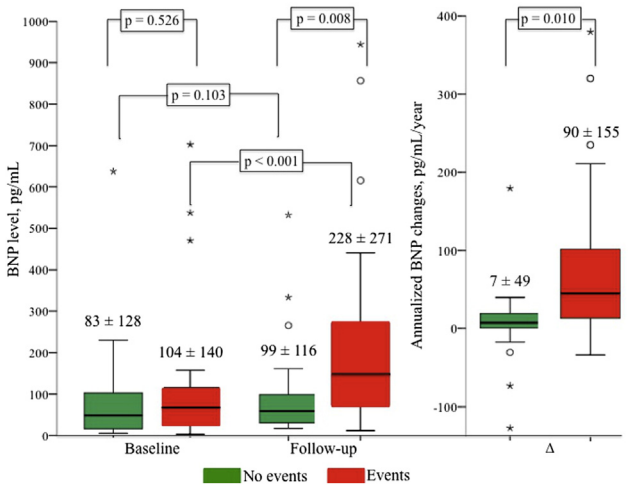

Figure 1. Comparison of baseline BNP, follow-up BNP, and annualized BNP changes (Δ) according to cardiac events.

can explain the discrepant results observed in the present cohort and previous published data, even by our group. Single BNP measurement provides a snapshot of the present clinical situation but not of the evolution of the disease, which is known to be highly individual. In contrast, the progression of AS and its repercussions on LV are prone to affect the BNP release over time with a gradual increase. Higher annualized BNP changes can be the sign of the progressive exhaustion of LV adaptation to the increased afterload, which precedes the occurrence of symptoms. Of note, in our cohort, indexed LA area, a sensitive marker of elevated LV filling pressure,[21] was an independent determinant of annualized BNP changes.

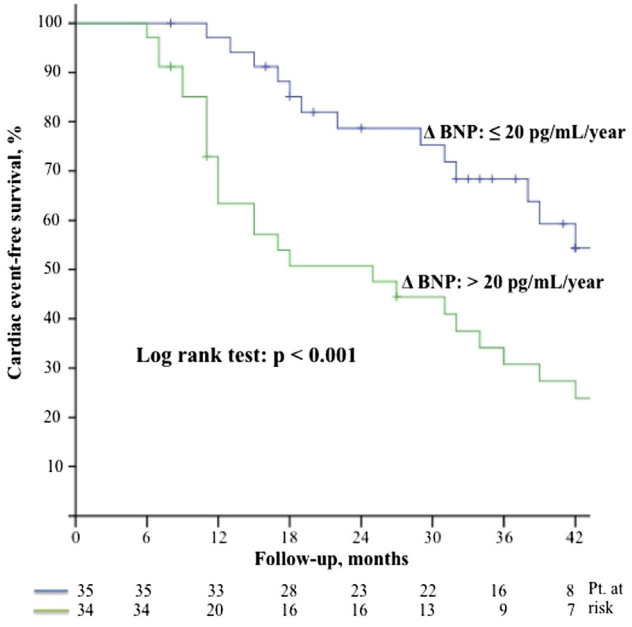

Figure 2. Event-free survival according to the median of annualized BNP changes.

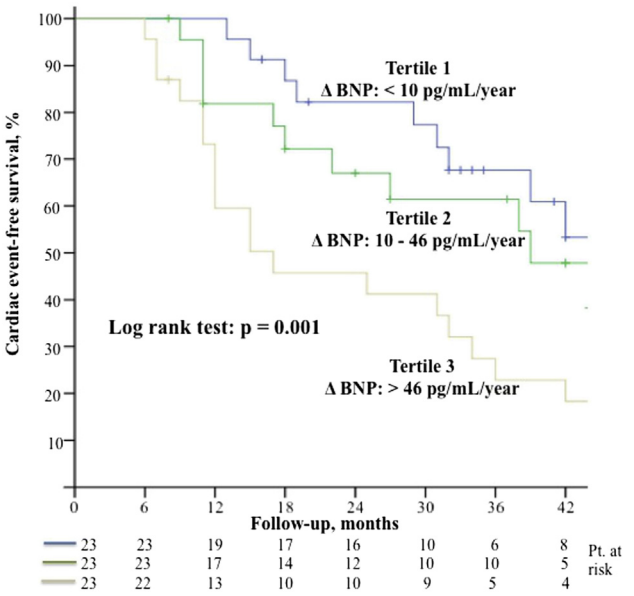

Figure 3. Event-free survival according to tertiles of annualized BNP changes.

Serial BNP changes and outcome in AS

In patients with AS, the prognostic value of single BNP level measurement has been largely demonstrated. Different cutoff values, ranging from 61 to 130 pg/mL, have been related to the occurrence of symptoms, need for aortic valve replacement, and cardiac-related death.[9-11] To note, those cutoff values were not adjusted to counteract the interindividual variation of BNP levels related to age and gender. To address this issue, Clavel et al. have shown that BNP normalized to age and sex was also highly predictive of outcomes in a large cohort.[22] However, there are few data regarding serial BNP changes for predicting outcome in asymptomatic patients with AS and preserved LVEF. In a small cohort of 29 asymptomatic patients with moderate-to-severe AS, the average rate of increase in the NT-proBNP level was greater in patients who developed symptoms compared with those who remained asymptomatic (+26 vs +7.2 pmol/L; $P = 0.014$).[17] Similarly, in a group of 43 initially asymptomatic patients, a mean BNP increase from 188 to 486 pg/mL was noticed in 14 patients developing

Table 3. Cox proportional hazard regression analysis for the prediction of adverse cardiac events according to median of annualized B-type natriuretic peptide changes

	BNP > 20 pg/mL/y		
Analysis	HR	95% CI	*P*
Univariable	3.48	1.81-6.69	< 0.001
Sex and baseline BNP-adjusted	3.48	1.81-6.69	< 0.001
Age- and dysl.-adjusted	3.49	1.77-6.86	< 0.001
Echo-adjusted	2.56	1.23-5.34	0.012
Age-, dysl., and echo-adjusted	2.73	1.27-5.86	0.010

Echocardiographic variables included in the model were peak aortic velocity and indexed left atrial area.

BNP, B-type natriuretic peptide; CI, confidence interval; dysl., dyslipidemia; HR, hazard ratio.

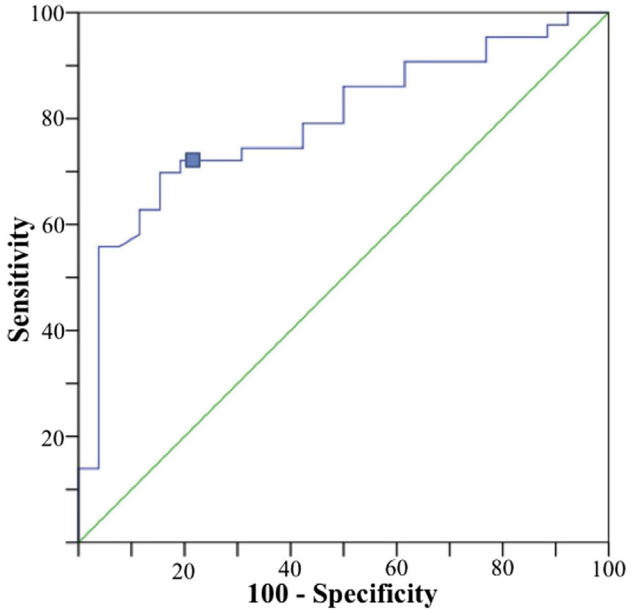

Figure 4. Receiver operating characteristic curve analysis for the prediction of adverse cardiac events using annualized BNP changes. Annualized BNP changes > 20 pg/mL/y (**blue square**) showed a good sensitivity of 71%, specificity of 77%, and an area under the curve of 0.79.

symptoms compared with no significant changes in stable one.[9] Unfortunately, in both studies, time-dependent analysis and cofactors associated with changes in the serial BNP level were not assessed. Our results are the first to demonstrate that patients with higher annualized BNP changes (>20 pg/mL/y) had a significantly lower cardiac event-free survival multiplied by 2.73 the risk of cardiac events, even after adjustment for cofactors. Moreover, only those patients experiencing a cardiac event had a significant increase in BNP level from baseline to follow-up, without any differences in BNP at baseline.

Clinical implications

Early recognition of symptoms in asymptomatic patients with moderate-to-severe AS and preserved LVEF is essential according to the associated worse individual prognosis justifying the immediate referral for aortic valve replacement. As the most common initial symptom is dyspnea (i.e., a nonspecific and subjective symptom), serial BNP changes, an independent predictor of cardiac events in our study, may help to define the best timing of aortic valve replacement. To note, the only other independent predictor of cardiac events identified in our cohort was the indexed LA area, already associated with a worse outcome in a previous study.[15] Hence, it might be useful to assess an individual baseline BNP level and then monitor the serial BNP changes.[23] An increase in serial BNP levels can identify patients with a more rapid disease process who could develop symptoms and may benefit form an "early surgery" strategy. Moreover, a parallel can be established between echocardiographic assessment of AS progression and serial BNP measurements. In fact, the progression of AS severity, using aortic jet velocity, has been shown to be quite variable among patients, as serial BNP measurements in our cohort. The rate of progression of stenosis was significantly higher in patients who presented cardiac events than those did not.[24] However, AS severity assessment using Doppler echocardiography requires experienced sonographers who are aware of technical pitfalls, compared with BNP level measurement being reproducible, low cost, and not operator dependent. In our cohort, a cutoff value of annualized BNP changes > 20 pg/mL/y provided a sensitivity and specificity of 71% and 77%, respectively, to predict the occurrence of events. We believe that serial BNP measurements should be integrated into the AS management algorithm as complement to clinical and echocardiographic evaluation.[23] However, further larger studies addressing mortality reduction after aortic valve replacement guided by serial BNP changes are needed to confirm the benefit of this strategy.

Limitations

The duration of follow-up and the interval between BNP measurements were not standardized in the entire cohort as individual management was left to the discretion of the cardiologist. The use of annualized BNP changes may partially temper such limitation. Furthermore, all patients were followed up in our heart valve clinic and received standard clinical management. We cannot exclude that other factors, such as medical therapy or changes in renal function, might have influenced the BNP changes. The majority of the reported cardiac events were aortic valve replacement indicated by symptoms for which the evaluation remains subjective. However, the occurrence of symptoms is a current class I indication for surgery and reflects general practice.

Conclusions

In our cohort of asymptomatic patients with AS and preserved LVEF, higher annualized BNP changes (> 20 pg/mL/y) were associated with a significantly lower cardiac event-free survival multiplied by 2.73 the risk of cardiac events. Moreover, compared with patients remaining free from a cardiac event, those experiencing a cardiac event had a progressive increase in BNP level from baseline to follow-up despite the absence of significant differences in BNP at baseline. Consequently, serial BNP changes may be useful to anticipate the development of class I indication for aortic valve replacement and to predict outcome.

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Disclosures

The authors have no conflicts of interest to disclose.

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