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Prospective Validation of the Prognostic Usefulness of B-Type Natriuretic Peptide in Asymptomatic Patients With Chronic Severe Aortic Regurgitation

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Objectives The purpose of this study was to determine the independent and additive prognostic value of B-type natriuretic peptide (BNP) in patients with severe asymptomatic aortic regurgitation and normal left ventricular function.

Background Early surgery could be advisable in selected patients with chronic severe aortic regurgitation, but there are no uniform criteria to identify candidates who could benefit from this strategy. Assessment of BNP has not been studied for this purpose.

Methods We prospectively evaluated 294 consecutive patients with severe asymptomatic organic aortic regurgitation and left ventricular ejection fraction above 55%. The first 160 consecutive patients served as the derivation cohort and the next 134 patients served as a validation cohort. The combined endpoint was the occurrence of symptoms of congestive heart failure, left ventricular dysfunction, or death at follow-up.

Results The endpoint was reached in 45 patients (28%) of the derivation set and in 35 patients (26%) of the validation cohort. Receiver-operator characteristic curve analysis yielded an optimal cutoff point of 130 pg/ml for BNP that was able to discriminate between patients at higher risk in both cohorts. BNP was the strongest independent predictor by multivariate analysis in the derivation set (odds ratio: 6.9 [95% confidence interval: 2.52 to 17.57], $p < 0.0001$) and the validation set (odds ratio: 6.7 [95% confidence interval: 2.9 to 16.9], $p = 0.0001$).

Conclusions Among patients with severe asymptomatic aortic regurgitation and normal left ventricular function, BNP ≥130 pg/ml categorizes a subgroup of patients at higher risk. Because of its incremental prognostic value, we believe BNP assessment should be used in the routine clinical evaluation of these patients. (J Am Coll Cardiol 2011; 58:1705–14) © 2011 by the American College of Cardiology Foundation

Severe organic aortic regurgitation (AR) is a progressive disease with a high incidence of events, especially after the onset of symptoms (1–5). Currently, consideration of surgical treatment in patients with severe AR involves the presence of symptoms of congestive heart failure (CHF) or abnormal resting left ventricular (LV) function (1,2,6,7). By contrast, the decision to intervene in asymptomatic patients without left ventricular dysfunction (LVD) ("early" surgery) is a source of ongoing clinical controversy. Early surgical treatment may be convenient for selected patients, but the risk of the surgical procedure should be considered against the risk of sudden death, heart failure, or LVD (1,2).

In this particular subset of patients, there are no strong indicators useful for the recommendation of early surgical intervention (1,2,8). Data have suggested a role for the assessment of serial echocardiographic parameters. Specifically, end-systolic diameter (ESD) and end-diastolic diameter (EDD), as well as LV volumes and ejection fraction (EF), have been found to allow risk stratification in asymptomatic patients (1–5). Another marker of hemodynamic consequences, the effective regurgitant orifice area (EROA), has also been shown to correlate with an adverse outcome (7).

In previous studies (9–11), the measurement of natriuretic peptides in patients with heart failure has become important. The B-type natriuretic peptide (BNP) and its inactive N-terminal pro–B-type natriuretic peptide (NT-proBNP) both result from the breakdown of proBNP. These hormones have vasodilator and diuretic effects, are antagonists of the adrenergic and renin-angiotensin systems, and are released in response to an increase in myocardial wall stress (WS) (1). The prognostic value of natriuretic peptides has been assessed in

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Abbreviations and Acronyms

AR = aortic regurgitation
BNP = B-type natriuretic peptide
CHF = congestive heart failure
CI = confidence interval
EDD = end-diastolic diameter
EDD/BSA = end-diastolic diameter indexed according to body surface area
EF = ejection fraction
EROA = effective regurgitant orifice area
ESD/BSA = end-systolic diameter indexed according to body surface area
HR = hazard ratio
IDI = integrated discrimination improvement
IQR = interquartile range
LV = left ventricular
LVD = left ventricular dysfunction
LVDSD = left ventricular systolic dysfunction symptoms or death
MET = metabolic equivalent
NT-proBNP = N-terminal pro–B-type natriuretic peptide
OR = odds ratio
PWTd = posterior wall thickness in diastole
PWTs = posterior wall thickness in systole
ROC = receiver-operator characteristic
RV = regurgitant volume
SBP = systolic blood pressure
WS = wall stress

patients with valve disease, with inconsistent results and without information regarding clinical and echocardiographic data (12,13).

Hence, the purpose of this investigation was to determine the additional prognostic value of baseline BNP level in asymptomatic patients with severe AR and no LVD. Our goal was also to validate prospectively a cutoff BNP value for the prediction of an adverse outcome, and to assess the prognostic significance of the changes in the BNP level observed between baseline and 1 year of follow-up.

Methods

Study population. In this single-center study, we prospectively evaluated 294 consecutive patients presenting with chronic severe asymptomatic organic AR and normal left ventricular performance (EF above 55%).

Applying a splitting technique, the first 160 consecutive patients were analyzed as the derivation set of data (mean age 51 ± 9 years; 64% men; mean EF 63 ± 5%) and the next 134 consecutive patients as the validation set (mean age 53 ± 10 years; 65% men; mean EF 64 ± 6%). In the derivation set, the etiology of the AR was degenerative in 72 patients, congenital (bicuspid) in 60, rheumatic in 12, post-endocarditis in 10, and miscellaneous in 6 patients. In the validation set, these etiologies were observed in 65, 51, 9, and patients, and miscellaneous in 3 patients. The miscellaneous etiologies in both groups were as follows: ankylosing spondylitis (n = 2), syphilis (n = 2), systemic lupus erythematosus (n = 1), myxomatous proliferation of the aortic valve (n = 1), rheumatoid arthritis (n = 1), quadricuspid valve (n = 1), and Crohn's disease (n = 1).

The underlying mechanism of AR was: degenerative (with valve thickening, annular enlargement, and central defect) (n = 137), bicuspid (n = 111) (incomplete closure with [n = 41] or without prolapse [n = 70]), rheumatic (with fibrosis preventing cusp apposition with a defect in the center of the valve) (n = 21), post-endocarditis (n = 16) (infection causing leaflet destruction or perforation in 10 patients), vegetation interfering with proper coaptation of the cusps (n = 6), combined (n = 7), and miscellaneous (n = 9).

We included patients fulfilling the following criteria: 1) chronic severe AR as determined by echocardiographic measurement (EROA ≥30 mm^2 and regurgitant volume [RV] ≥60 ml/beat) (14); 2) preserved exercise tolerance defined by an exercise electrocardiogram performed with the Bruce protocol and the following requirements: functional capacity ≥7 metabolic equivalents (METs) without symptoms (angina or dyspnea) or any of the following: complex ventricular arrhythmia, hypotension, or pathological ST segment deviation; and 3) LVEF above 55% at rest. We excluded patients with associated valve disease (aortic stenosis with peak gradient ≥20 mm Hg, moderate or severe mitral regurgitation, hemodynamically significant mitral stenosis, or significant right-sided organic valve disease), previous valve or coronary surgery, aortic root enlargement (≥40 mm), aortic dissection or ongoing endocarditis, cardiomyopathies or pericardial diseases, and a history of coronary artery disease.

Follow-up was complete in all but 3 patients (2 patients of the derivation set and 1 patient of the validation set).

Clinical data. At entry, complete clinical evaluation was performed in all patients. Decisions about valve surgery were left to the treating physicians, who were unaware of the BNP results.

Echocardiographic data. All studies were performed with Hewlett Packard Sonos 5500 equipment (Andover, Massachusetts). Studies included a spectral, continuous, and color Doppler transthoracic echocardiographic examination in all patients. The degree of AR was quantified according to the classical color Doppler parameters (14). LV volume and LVEF were measured by using Simpson's biplane technique (15). EDD and ESD were indexed according to body surface area (EDD/BSA and ESD/BSA) (16). Atrial volume was indexed by body surface area; mean systolic WS and pulmonary artery systolic pressures were measured classically (17). We determined RV, regurgitant fraction, and EROA as averaged values measured with the quantitative Doppler flow method and the proximal isovelocity surface area method that analyzes proximal flow convergence (18,19).

End-diastolic radius/thickness ratio was calculated as: EDD/(2 × PWTd), where PWTd is posterior wall thickness in end-diastole. A previous study (20) reported that this index is linearly related to the LV volume/mass ratio, as a measure of LV pre-load.

End-systolic circumferential WS, as a measure of LV afterload, was calculated as: (0.334 × SBP × LVDs)/(PWTs [1 × PWTs/LVDs]) (kdyne/cm^2), where SBP is systolic blood pressure and PWTs is posterior wall thickness in systole (21).

The echocardiographic readings were conducted by 2 independent observers who were blinded to the clinical and biochemistry information.

Biochemistry data. Blood samples were obtained in all patients 24 h after enrollment in the echocardiography laboratory and then repeated 1 year later. Venous blood samples were obtained on usual medications with the patient resting quietly while semirecumbent. The samples were placed immediately on ice, and plasma was stored at −80°C before being assayed for BNP using standard radioimmunoassay (22). The samples were obtained by technicians blinded to the clinical and echocardiographic data. All BNP measurements were carried out at the same time.

Endpoint definition. The combined endpoint consisted of the appearance of either CHF or LVD, or left ventricular systolic dysfunction symptoms or death (LVDSD) during follow-up. The presence of CHF was defined as the onset of dyspnea in New York Heart Association functional class III and IV requiring initiation of sustained pharmacologic treatment. New onset of LVD was defined as the assessment of an LVEF below 55% during follow-up (1,23,24) that was not present at baseline.

All outcomes were assessed by 2 investigators blinded to the echocardiographic and clinical data. Patients referred for surgery without symptoms or low EF (because of physician preferences) were counted as not reaching an endpoint in the analysis, and these cases were censored.

Follow-up. Clinical and echocardiographic evaluations were performed at least yearly during a follow-up visit. Patients who died or underwent surgery were censored the same day and all others were censored at the end of follow-up.

Statistical analysis. All results for continuous variables are expressed as mean ± SD, and skewed variables are expressed as median (25% to 75% interquartile range [IQR]). For group-wise comparisons of continuous variables, the Mann-Whitney *U* test and Student *t* test were used for skewed and normally distributed variables, respectively. For categorical variables, the Fisher exact or chi-square tests were used. The cutoff level for each variable was set according to the receiver-operator characteristic (ROC) analysis. The cutoff level for BNP was set according to the ROC curve. The BNP value showing the maximum likelihood ratio in the curve was established as the cutoff point between low and high BNP. This cutoff point was prospectively tested in the validation set.

Survival analysis was assessed using the Kaplan-Meier method. Nonadjusted comparison of time to the event was based on the log-rank test. Logistic regression multivariate analysis was developed to analyze the effect of clinical and echocardiographic variables on the observed association between basal BNP levels and the risk of the combined endpoint. For the assessment of linearity, we grouped BNP concentrations and the echocardiographic variables into quartiles. We then fitted a regression model for the prediction of the combined endpoint, with the lowest quartile serving as the reference group, and plotted the average value of each quartile versus the coefficient of the quartile. The plot was then examined with respect to the shape of the resulting curve. Variables showing lack of linearity were logarithmically transformed.

The multivariate regression models incorporated clinical and echocardiographic variables that proved to be related to the combined endpoint on univariate analysis. To assess the statistical significance of BNP values, we adjusted the p values using the Bonferroni correction, dividing the usual p value (0.05) by the number of variables in the model.

To facilitate the clinical interpretation, we repeated the multivariate analysis, entering BNP and the echocardiographic measurements as dichotomous variables with the cutoff points that were previously described.

Comparison between ROC curves was performed with the ROC analyzer program, Stata version 10.0 (Stata Corporation, College Station, Texas).

To assess the usefulness of BNP, we determined the integrated discrimination improvement (IDI), absolute and relative, to quantify the increase in separation of events and nonevents as determined by Pencina et al. (25). The statistical analysis was performed with Stata version 10.0 (Stata Corporation, College Station, Texas). A p value <0.05 was considered significant, and all of the tests performed were 2-tailed.

Results

Baseline characteristics. A total of 294 patients were included, 160 in the derivation cohort and 134 in the validation cohort. Median BNP values at entry were similar in both sets: 31 (IQR: 7 to 244) and 35 (IQR: 9 to 234) in the derivation and validation cohorts, respectively.

The characteristics of both sets of 294 patients were as follows: age 53 ± 9 years; 165 patients (56%) were male; 138 had prior hypertension (47%); median EF was 0.65 (IQR: 0.61 to 0.72); median EDD/BSA was 40 (IQR: 28 to 44); median EDS/BSA was 18 (IQR: 13 to 27); median EROA was 48 (IQR: 39 to 78); and median RV was 79 (IQR: 63 to 101).

Events. In the derivation set, 45 patients (28%) suffered LVDSD. Three patients (1.9%) died; it was sudden in 2 patients and caused by congestive heart failure in 1 patient. New CHF was diagnosed in 29 patients (18%). Among these 29 patients, 22 required the initiation of sustained pharmacologic treatment for CHF, including 7 patients who required hospitalization for the same reason. Fifteen patients (9.4%) developed LVD. Seven patients (4.3%) had new-onset atrial fibrillation and 15 patients (9.4%) developed pulmonary hypertension. Mean follow-up of the derivation set was 46 ± 10 months.

Aortic valve surgery was performed in 50 (31%) patients at follow-up. Forty-four patients underwent surgery because of CHF or LV systolic dysfunction. The median BNP value in patients who underwent surgery was 139 (IQR: 90 to 209) versus 42 (IQR: 15 to 89) in patients without surgery.

Six patients did not reach the combined endpoint but underwent surgery, as indicated by their referring physician. These patients were not significantly different from patients who reached the combined endpoint in terms of their clinical and echocardiographic variables. The BNP values in this subset of 6 patients were median 31 pg/ml (IQR: 11 to 105 pg/ml).

In the validation set, 35 patients (26%) developed LVDSD. Two patients (1.5%) died; it was sudden in 1 patient and noncardiac related in the other. In addition, 26 patients (19.4%) developed CHF (17 patients received sustained pharmacologic treatment for CHF and 9 patients were hospitalized for the same reason). Finally, 14 patients (10.4%) developed LVD. Mean follow-up in the validation set was 38 ± 9 months. Five patients (3.7%) experienced new-onset atrial fibrillation, and 12 patients (9.0%) developed pulmonary hypertension during follow-up.

Aortic valve surgery was performed in 39 patients (29.1%) of the validation set. The BNP value in patients who underwent surgery was 137 (IQR: 93 to 210) versus 45 (IQR: 11 to 83) in patients without surgery. Seven patients did not reach the combined endpoint but underwent surgery, as indicated by their referring physician. These patients were not significantly different with regard to clinical and echocardiographic variables from patients who reached the combined endpoint, and the median BNP value in these 7 patients was 36 (IQR: 11 to 99).

Predictive value of BNP. UNIVARIATE ANALYSIS. The median BNP values were higher in patients who suffered LVDSD, in both the derivation (149 [IQR: 92 to 217] vs. 48 [IQR: 17 to 83], $p = 0.001$) and the validation (141 [IQR: 87 to 210] vs. 42 [IQR: 12 to 79], $p = 0.001$) sets.

When we stratified BNP levels according to quartiles (≤35, 36 to 79, 80 to 129, and ≥130 pg/ml), in the derivation set patients' event-free survival at 60 months was as follows: 99 ± 4%, 96 ± 7%, 90 ± 6%, and 34 ± 8%, respectively ($p < 0.0001$).

The areas of the ROC curves relating baseline BNP levels to the combined endpoint were 0.84 ± 0.06 and 0.82 ± 0.05 in the derivation and validation cohorts, respectively. From the ROC curve of the derivation set, we were able to derive an optimal cutoff value of 130 pg/ml. The highest likelihood ratio corresponding to that value was 5.8 (95% confidence interval [CI]: 2.6 to 11.6). In the ROC curve of the validation set, a BNP value of 130 pg/ml was also associated with the best likelihood ratio of the combined endpoint.

Baseline characteristics of patients according to BNP levels at admission are compared in Table 1. No significant differences were observed in either set in terms of age, sex, hypertension, atrial fibrillation, or heart rate. All parameters related to the amount of AR—such as RV, regurgitant fraction, and EROA—were also significantly higher in patients with elevated BNP in the derivation set, as well as in the validation set.

In the Kaplan-Meier analysis, BNP values were dichotomized at this cutoff point and allowed to discriminate patients with higher risk of LVDSD in the derivation set (log-rank test 11.7; adjusted hazard ratio [HR]: 6.7 [95% CI: 2.3 to 15.6], $p < 0.0001$) and also in the validation set (log-rank test 12.2; adjusted HR: 6.54 [95% CI: 2.2 to 16.3], $p < 0.0001$) (Figs. 1A and 1B).

Applying this cutoff value, sensitivity, specificity, negative predictive value, and positive predictive value to predict LVDSD in the derivation set were 78%, 93%, 91%, and 83%, respectively, while in the validation set values were 77%, 94%, 91%, and 81%, respectively.

Table 2 shows the relationship between baseline variables and prognosis. In both sets, univariate markers of worse evolution were BNP, ESD/BSA, EDD/BSA, EROA, atrial volume indexed by body surface area, age, pulmonary artery systolic pressures, EF, and LV volumes. Neither the mechanism of the AR nor the medical treatments were associated with the outcome.

MULTIVARIATE ANALYSIS. In the derivation set, all variables significantly associated with the endpoint were included in a logistic regression analysis. In our first model, we used log transformation of the continuous variables. In the derivation cohort, the independent predictors were: BNP (odds ratio [OR]: 6.89 [95% CI: 2.52 to 17.57], $p < 0.0001$), ESD/BSA (OR: 3.14 [95% CI: 1.82 to 15.92], $p < 0.01$), and EROA (OR: 3.87 [95% CI: 2.27 to 16.45], $p < 0.001$). According to this model, the absolute and relative IDI of the variables were as follows: BNP, 0.091078 and 0.198 ($p < 0.00001$); ESD/BSA, 0.058237 and 0.083 ($p < 0.001$); and EROA, 0.078125 and 0.117 ($p < 0.0001$).

When we entered all markers in the multivariate model as categorical variables, BNP ≥130 pg/ml was the strongest independent predictor of symptoms, LVD, and/or death (OR: 6.9 [95% CI: 2.52 to 17.57], $p < 0.0001$). Other independent prognostic variables were: ESD/BSA ≥24 mm/m^2 (OR: 3.4 [95% CI: 1.88 to 11.9], $p < 0.01$); and EROA ≥50 mm^2 (OR: 4.3 [95% CI: 2.4 to 12.4], $p < 0.001$) (Table 3). In addition, BNP ≥130 pg/ml was the strongest predictor of isolated LVD (OR: 6.6 [95% CI: 2.3 to 22.4], $p < 0.0001$). Another independent predictor of LVD was an EROA ≥50 mm^2 (OR: 4.9 [95% CI: 2.1 to 27.7], $p < 0.001$).

In the validation set, multivariate analysis determined that the following variables were independent predictors: BNP ≥130 pg/ml (OR: 6.7 [95% CI: 2.9 to 16.9], $p = 0.0001$), EROA ≥50 mm^2 (OR: 4.3 [95% CI: 2.6 to 13.5], $p = 0.001$); and ESD/BSA >24 mm/m^2 (OR: 3.4 [95% CI: 1.7 to 14.7], $p < 0.02$). According to this model, the absolute and relative IDI of the variables were: BNP, 0.089174 and 0.187 ($p < 0.00001$); ESD/BSA, 0.053139 and 0.078 ($p < 0.001$), and EROA, 0.076457 and 0.115 ($p < 0.0001$). BNP ≥130 pg/ml was the strongest predictor of isolated LVD (OR: 6.2 [95% CI: 2.5 to 27.3], $p < 0.0001$). Another independent predictor of LVD was EROA ≥50 mm^2 (OR: 4.8 [95% CI: 2.2 to 29.4], $p < 0.001$).

The addition of BNP to the non-BNP model (EROA, ESD/BSA, and EDD/BSA) significantly increased the area

Table 1 Basal Characteristics in Relation to BNP Levels

Characteristic	Derivation Set			Validation Set		
	BNP <130 pg/ml (n = 118)	BNP ≥130 pg/ml (n = 42)	p Value	BNP <130 pg/ml (n = 100)	BNP ≥130 pg/ml (n = 34)	p Value
Age (yrs)	51 ± 9	56 ± 10	0.07	52 ± 9	57 ± 8	0.08
Male (%)	65 (55)	24 (57)	0.11	54 (54)	18 (52)	0.94
AF (%)	5 (4)	3 (7)	0.04	4 (4)	2 (6)	0.045
Hypertension (%)	64 (54)	17 (40)	0.19	55 (55)	14 (42)	0.16
SBP (mm Hg)	139 ± 37	136 ± 21	0.58	136 ± 21	135 ± 25	0.91
Diastolic blood pressure (mm Hg)	61 ± 12	56 ± 14	0.48	59 ± 10	55 ± 12	0.56
Heart rate (beats/min)	76 ± 10	69 ± 11	0.21	78 ± 10	72 ± 12	0.37
Exercise capacity (METs)	9.5 (8.5–15)	8.5 (8.0–12.5)	0.37	10 (8.0–14)	8.5 (7.5–13.5)	0.15
Heart-rate product (×1,000) at peak exercise test	22.4 (18.7–25.8)	21.8 (17.9–24.7)	0.61	21.9 (17.8–25.7)	20.8 (17.4–24.9)	0.49
SBP (mm Hg) at peak exercise	174 (135–198)	171 (138–194)	0.77	176 (137–209)	172 (139–205)	0.64
Heart rate (beats/min) at peak exercise	121 (97–144)	119 (94–141)	0.81	123 (96–147)	120 (94–142)	0.87
EF (%)	64 (57–71)	61 (56–65)	0.035	65 (58–70)	62 (57–65)	0.04
EDV (ml/m^2)	97 (56–107)	125 (69–143)	0.03	95 (55–105)	119 (61–136)	0.025
ESV (ml/m^2)	27 (17–34)	35 (24–40)	0.02	25 (18–32)	34 (22–39)	0.02
Fractional shortening (%)	38 (33–44)	35 (31–39)	0.06	39 (34–46)	35 (32–37)	0.056
EDD/BSA (mm/m^2)	30 (27–36)	42 (28–47)	0.001	32 (28–37)	40 (31–45)	0.01
ESD/BSA (mm/m^2)	16 (12–21)	26 (18–30)	0.001	15 (13–22)	24 (20–27)	0.001
R/T	2.35 (1.7–2.6)	2.52 (1.91–3.11)	0.02	2.38 (1.65–2.55)	2.49 (1.87–3.07)	0.03
WS (kdyne/cm^2)	64.4 (37.4–73.1)	73.2 (42.7–83.6)	0.02	63.1 (38.4–71.2)	71.4 (40–81.3)	0.03
RV (ml/beat)	74 (63–90)	87 (69–107)	0.01	76 (62–91)	91 (69–105)	0.01
RF (%)	59 (53–77)	69 (59–84)	0.01	61 (53–76)	70 (56–88)	0.01
EROA (mm^2)	44 (35–69)	57 (41–84)	0.0001	45 (34–66)	62 (48–91)	0.001
AV/BSA (cm^3/m^2)	57 (37–68)	65 (48–75)	0.02	54 (34–62)	63 (39–79)	0.04
PASP (mm Hg)	25 (18–31)	33 (22–40)	0.035	23 (15–29)	34 (21–42)	0.025
Medical treatment during the study (%)						
ACE-I	68 (57)	21 (50)	0.21	50 (50)	16 (47)	0.69
ARB	27 (23)	11 (26)	0.47	23 (23)	7 (20)	0.52
CCB	19 (16)	7 (17)	0.93	16 (16)	6 (18)	0.71
AA	5 (4.2)	2 (4.7)	0.77	4 (4)	1 (3)	0.74
BB	6 (5)	2 (4.7)	0.87	4 (3)	1 (3)	1.00
Digoxin	3 (2.5)	1 (2.4)	0.82	2 (2)	1 (3)	0.56

Values are mean ± SD, absolute numbers (%), or median (Interquartile range).

AA = aldosterone antagonists; ACE-I = angiotensin-converting enzyme inhibitors; AF = atrial fibrillation; ARB = angiotensin II receptor blocker; AV/BSA = atrial volume/body surface area; BB = beta-blockers; BNP = B-type natriuretic peptide; CCB = calcium-channel blockers; EDD/BSA = end-diastolic diameter/body surface area; EDV = end-diastolic volume; EF = ejection fraction; EROA = effective regurgitant orifice area; ESD/BSA = end-systolic diameter/body surface area; METs = metabolic equivalents; PASP = pulmonary artery systolic pressure; RF = regurgitant fraction; R/T = end-diastolic radius/thickness ratio; RV = regurgitant volume; SBP = systolic blood pressure; WS = end-systolic circumferential wall stress.

under the ROC curve from 0.82 to 0.92 (p = 0.01) in the derivation set, and from 0.80 to 0.89 (p = 0.01) in the validation set (Fig. 2A and 2B). The combination of BNP and EROA information in the derivation set is depicted in Figure 3. For comparison, values corresponding to the combination of EROA <50 mm^2 and BNP <130 pg/ml were chosen as the reference group. As shown, the association of BNP levels ≥130 pg/ml and EROA ≥50 mm^2 entailed the worst prognosis. Among these patients, 24 (88%) had LVSD (HR: 4.7 [95% CI: 2.6 to 15.8], p < 0.0001 vs. reference group). Of note, of the 3 deaths observed in the study, 2 occurred in this subgroup.

Serial BNP measurements. Patients who reached an endpoint had a higher rate of increase in BNP levels at 1 year than patients with an uneventful course (derivation set 29 ± 10 pg/ml vs. 10 ± 6 pg/ml, p= 0.0001; validation set 31 ± 7 pg/ml vs. 9 ± 4 pg/ml, p = 0.001).

Among patients with baseline BNP values <130 pg/ml, 4 (2.5%) exhibited a BNP elevation above that level at 1 year in the derivation set, and 3 patients (2.2%) did so in the validation set. All of these patients had LVDSD at follow-up.

By Kaplan-Meier analysis, patients with an increased BNP ≥130 pg/ml at 1 year had a worse outcome than patients who persisted with BNP <130 pg/ml (log-rank test 16.2; adjusted HR: 7.6 [95% CI: 4.2 to 19.6], p < 0.0001). Similar findings were observed in the validation set (log-rank test 15.8; adjusted HR: 8.6 [95% CI: 3.5 to 19.8], p < 0.0001).

Discussion

In this population of asymptomatic patients with severe AR and normal LV systolic function, baseline BNP level was a strong independent prognostic marker. Our study also confirmed that in this type of patient, echocardiographic

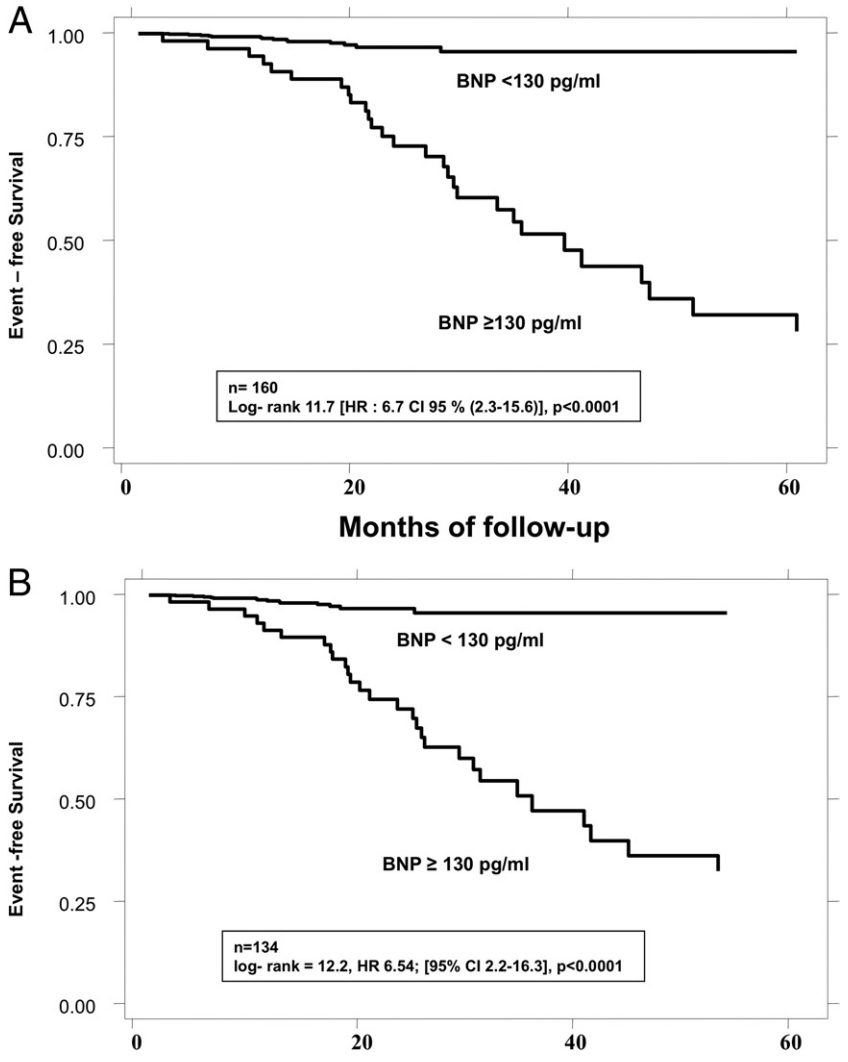

Figure 1 Patient Risk of LVDSD According to BNP Levels

(A) Derivation set; **(B)** validation set. BNP = B-type natriuretic peptide; CI = confidence interval; HR = hazard ratio; LVDSD = left ventricular systolic dysfunction symptoms or death.

parameters such as ESD and EROA are also independent predictors of adverse outcome. However, according to our results, BNP was of greater prognostic value than ESD or EROA, and contributed independent prognostic information in additional to that provided by these echocardiographic parameters. As shown, after the addition of BNP to the echocardiographic model, the area under the ROC curve increased significantly both in the derivation and the validation sets. Furthermore, we determined and validated an optimal cutoff point for BNP of 130 pg/ml, thereby identifying asymptomatic patients with severe AR and preserved LV systolic function who are at higher risk. In our study, BNP ≥130 pg/ml predicted a worse outcome with additional information barely affected by the adjustments for EDD, ESD, WS, and EROA. Another point to consider is the value of the repeated measurements of BNP. Patients with a greater BNP increase at 1 year had a worse subsequent course.

According to these data, the average time elapsed between the finding of an elevated BNP and the events was 15 months. Hence, the clinical application of this criterion to avoid exposing the patient to the greater risk of the pre-symptomatic phase would imply anticipating the surgical indication in approximately 2 years.

As stated by current guidelines (1,3), patients with severe AR complicated with heart failure or LV systolic dysfunction should be promptly referred for surgical treatment. Alternatively, clinical surveillance with frequent reassessment is the preferred therapeutic strategy for asymptomatic patients with preserved LV function (1,3). However, the

Table 2 Univariate Predictors of LVDSD

Characteristic	Derivation Set (n = 160)		Validation Set (n = 134)	
	OR (95% CI)	p Value	OR (95% CI)	p Value
Age >60 yrs	1.9 (1.4–7.2)	0.02	1.4 (1.1–8.2)	0.04
EF ≤60%	2.0 (1.27–11.8)	0.036	2.1 (1.21–12.8)	0.035
EDV/BSA ≥90 ml/m^2	1.75 (1.05–12.5)	0.045	1.7 (1.1– 13.4)	0.04
ESV/BSA ≥35 ml/m^2	2.1 (1.3–10.1)	0.031	2.05 (1.32–12.4)	0.027
Fractional shortening <35%	1.97 (0.78–6.74)	0.21	1.84 (0.81–7.1)	0.34
AF	1.98 (0.89–8.9)	0.062	2.0 (0.93–9.4)	0.058
BNP ≥130 pg/ml	6.6 (2.9–16.6)	0.0001	6.7 (2.4–17.3)	0.0001
EDD/BSA ≥35 mm/m^2	2.2 (1.7–14.3)	0.01	2.0 (1.5–13.4)	0.02
ESD/BSA ≥24 mm/m^2	3.6 (2.1–10.4)	0.001	3.4 (1.7–11.5)	0.001
R/T ≥2.15	1.5 (1.02–7.8)	0.05	1.64 (1.3–8.9)	0.04
WS ≥65 kdyne/cm^2	1.98 (1.24–8.6)	0.03	2.15 (1.41–9.78)	0.025
RV ≥75 ml/beat	2.7 (1.3–10.2)	0.01	2.4 (1.2–13.1)	0.03
EROA ≥50 mm^2	4.4 (2.2–10.7)	0.0001	4.3 (2.4–11.7)	0.0001
AV ≥60 cm^3/m^2	2.4 (1.7–11.2)	0.01	2.3 (1.3–14.1)	0.02
PASP ≥35 mm Hg	1.92 (1.47–9.47)	0.03	1.7 (1.27–10.2)	0.035

CI = confidence interval; LVDSD = left ventricular systolic dysfunction symptoms or death; OR = odds ratio; other abbreviations as in Table 1.

potential advantages of early surgical treatment merit consideration (2,4,7). First, early surgery may prevent sudden death, which occurs in about 1% of cases. Second, early surgery may prevent the development of CHF or LV systolic dysfunction (2,6–8). This latter point is important because the presence of such complications is associated with a worse perioperative and post-operative outcome (2,5,24,25).

Although the early intervention is theoretically attractive, experience with this strategy is still scarce, probably due to the lack of strong prognostic markers that allow for identification of potential candidates for early surgery. In asymptomatic patients, previous studies have shown that echocardiographic parameters reflecting ventricular size and volume overload (EDD, ESD, and end-systolic volume), WS, and the EROA may identify patients who will be at greater future risk (7,26,27). The prospective studies of AR natural history with an average follow-up of 7 to 8 years found that systolic phase descriptors measured at rest and during exercise predicted heart failure, subnormal LVEF at rest, and sudden death (4,5,26). In addition, other important determinants of prognosis include EDD and stress-normalized LV performance (26,27).

However, according to our data, a marker of myocardial stress such as BNP is able to discriminate prognosis better than the echocardiographic parameters associated with the magnitude of volume overload or changes in resting systolic function, suggesting that BNP is not merely a surrogate of the volume overload imposed by the AR.

Table 3 Multivariate Analysis to Predict the Combined Endpoint: Derivation Set

Endpoint	OR (95% CI)	p Value
BNP ≥130 pg/ml	6.9 (2.52–17.57)	0.0001
ESD/BSA ≥24 mm/m^2	3.4 (1.88–11.9)	0.01
EROA ≥50 mm^2	4.3 (2.4–12.4)	0.001
EDD ≥35 mm/m^2	2.1 (0.88–13.7)	0.09

Abbreviations as in Tables 1 and 2.

Which are the mechanisms responsible for the prognostic significance of elevated BNP in this particular group of patients? Experimental and clinical data reinforce the hypothesis that higher BNP levels in patients with preserved LV function at rest could represent subclinical ventricular dysfunction (28,29). Thus, these data led us to speculate that elevations of this peptide in asymptomatic patients may indicate the presence of subtle myocardial impairment elicited by longstanding volume and pressure overload in AR.

There are only few data available regarding the prognostic value of natriuretic peptides in chronic AR (12,13). One study found that NT-proBNP was increased in conservatively treated patients and decreases after successful surgical therapy. The same study also underlines the consistent relation of NT-proBNP level with the severity of the aortic valve defect (12). In another study (13), natriuretic peptides (BNP and NT-proBNP) were higher in symptomatic than in asymptomatic patients but with a weak correlation of both markers with the echocardiographic measures of LV size and function (EDD, ESD, end-systolic volume, end-diastolic volume, LV systolic WS, and left atrial size).

Study limitations. In this study, functional capacity was assessed using an electrocardiographic exercise test. Other tests may be more accurate for this analysis, such as an exercise test with simultaneous measurement of myocardial oxygen consumption; however, current guidelines do not mention its usefulness (1,3). We also believe that the lack of tissue Doppler measurements and of an exercise stress echocardiogram may be considered a limitation of this study (30).

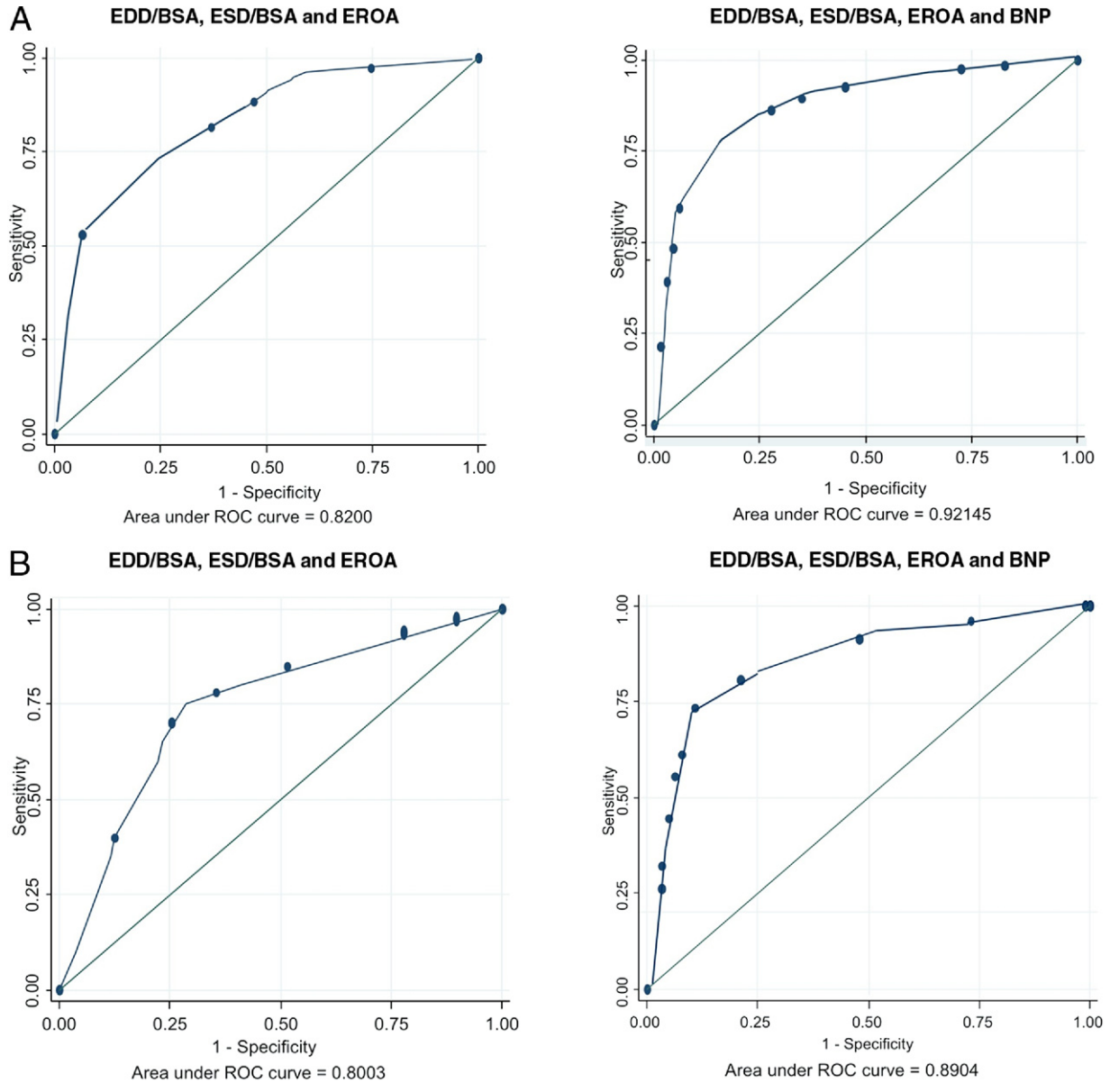

Figure 2 **ROC Analysis: Incremental Value of BNP When Added to Echocardiographic Variables in the Prediction of LVDSD**

EDD/BSA = end-diastolic diameter indexed according to body surface area; EROA = effective regurgitant orifice area; ESD/BSA = end-systolic diameter indexed according to body surface area; LVDSD = left ventricular systolic dysfunction, symptoms, or death; ROC = receiver-operator characteristic.

These results are not conclusive, and a randomized, controlled study between patients with early versus deferred study between patients with early versus deferred surgery stratified according to BNP level is needed to assess the clinical value and the cost/benefit implications of this strategy. Finally, we should mention that the model could be overfitted when applied to the validation set.

Conclusions

Careful clinical assessment and surveillance are mandatory in asymptomatic patients with severe AR and preserved LV function. Because of its strong independent and incremental prognostic value, BNP assessment—integrated with echo parameters of LV performance—should be considered in the clinical routine workup for risk stratification of patients with severe AR who are free of symptoms or LVD.

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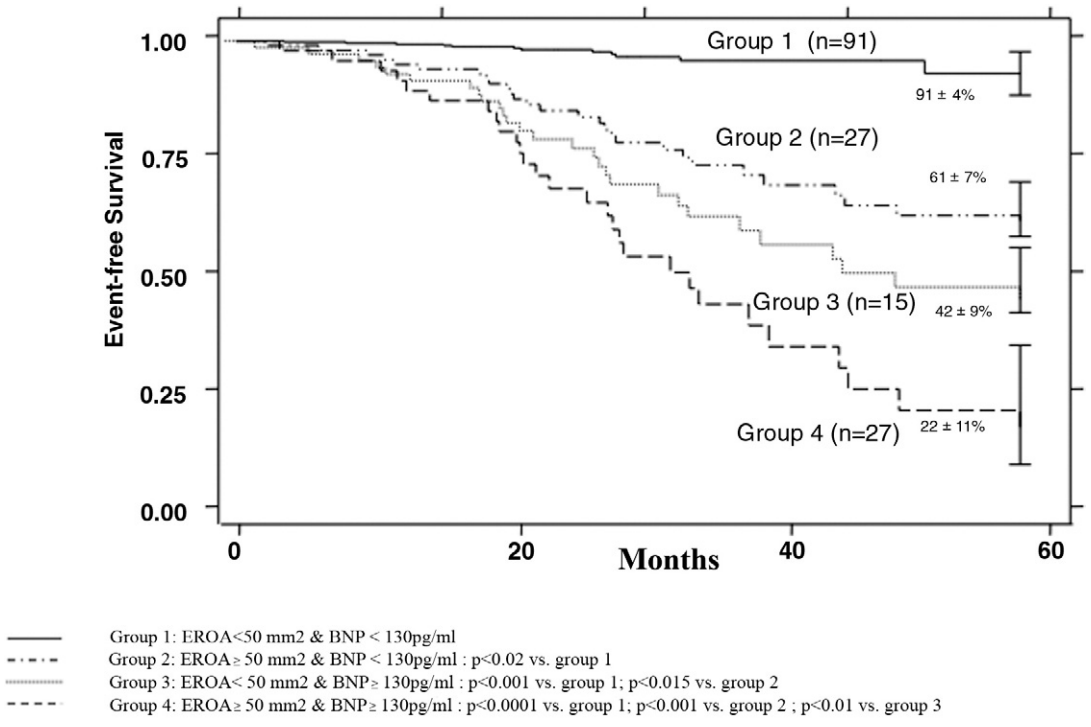

Figure 3 **Survival Free of LVDSD According to BNP in Combination With EROA Levels**

Patients' survival free of LVDSD in the derivation set (n = 160). Abbreviations as in Figure 2.

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