

# Prognostic Effect of Long-Axis Left Ventricular Dysfunction and B-Type Natriuretic Peptide Levels in Asymptomatic Aortic Stenosis

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In aortic stenosis (AS), the increased afterload results in progressive structural and functional changes that precede the development of symptoms. We hypothesized that the detection of abnormalities in left ventricular long-axis function could identify patients with asymptomatic AS at increased risk of events. We prospectively examined the outcome of 126 patients with asymptomatic AS who underwent a comprehensive echocardiographic examination, including tissue Doppler imaging. B-type natriuretic peptide (BNP) was measured in all patients. During a median follow-up period of  $20.3 \pm 17.8$  months, 6 patients died, 8 developed symptoms but did not undergo surgery, and 48 underwent aortic valve replacement. On multivariate Cox regression analysis, the parameters associated with the predefined outcome were gender ( $p = 0.048$ ), left atrial area index ( $p = 0.011$ ), systolic annular velocity ( $p = 0.016$ ), E/Ea ratio ( $p = 0.024$ ), late diastolic annular velocity ( $p = 0.023$ ), and BNP ( $p = 0.012$ ). Using receiver operating characteristics curve analysis, a left atrial area index of  $\geq 12.4 \text{ cm}^2/\text{m}^2$ , systolic annular velocity of  $\leq 4.5 \text{ cm/s}$ , E/Ea ratio  $> 13.8$ , late diastolic annular velocity of  $\leq 9 \text{ cm/s}$ , and BNP of  $\geq 61 \text{ pg/ml}$  were identified as the best cutoff values to predict events. In conclusion, in asymptomatic AS, tissue Doppler imaging and BNP measurements provide prognostic information beyond that from clinical and conventional echocardiographic parameters. © 2010 Elsevier Inc. All rights reserved. (Am J Cardiol 2010;105:383–388)

Aortic valve stenosis (AS) is the most common valvular disease and has become the most common cardiovascular disease, after coronary artery disease and hypertension, in developed countries.<sup>1</sup> AS is characterized by a long asymptomatic phase, lasting several decades, during which outflow obstruction progressively develops.<sup>2</sup> Aortic valve replacement is the sole effective therapy for symptomatic patients. In contrast, the management of asymptomatic AS remains controversial.<sup>3,4</sup> In these patients, the chronically increased afterload results in progressive left ventricular (LV) myocardial hypertrophy and interstitial fibrosis, diastolic dysfunction, elevated left atrial pressures, dilation of the left atrium, and, eventually, intrinsic myocardial dysfunction.<sup>5</sup> These structural and functional changes precede symptom development, predict changes in clinical status, and trigger B-type natriuretic peptide (BNP) release.<sup>6,7</sup> In AS, the BNP level correlates with the valve area, diastolic function, functional status, and symptomatic deterioration and might improve risk stratification.<sup>8–11</sup> Tissue Doppler measurement of mitral annular velocities is a sensitive method for the detection of early abnormalities in LV long-axis function and improves the assessment of LV diastolic function.<sup>12</sup> In asymptomatic AS, the incremental prognostic value of tissue Doppler imaging and BNP measurement

compared with validated parameters has never been investigated. The present study was undertaken to prospectively assess the comparative usefulness in predicting the clinical outcomes of long-axis function and BNP level in a series of patients with asymptomatic severe AS.

## Methods

Asymptomatic patients with severe AS were prospectively screened from our echocardiographic laboratory for inclusion in the present study. All the patients met the following criteria: (1) moderate to severe AS, as defined by an aortic valve area of  $\leq 1.2 \text{ cm}^2$ ; (2) no symptoms according to a careful history taken by the referring physician; (3) normal LV ejection fraction ( $\geq 55\%$ ), as calculated by 2-dimensional echocardiography; (4) no more than mild associated cardiac valve lesions; (5) sinus rhythm; and (6) serum creatinine  $< 16 \text{ mg/L}$ . A total of 126 patients met these criteria. The relevant institutional review boards approved the protocol, and all patients gave written informed consent.

A comprehensive Doppler echocardiographic study, including M-mode, 2-dimensional echocardiography, color Doppler, and pulsed-wave and continuous-wave Doppler measurements was performed, in all patients using a VIVID 7 ultrasound machine (General Electric Healthcare, Little Chalfont, United Kingdom). The images were stored on a dedicated workstation for off-line analysis. For each measurement,  $\geq 2$  cardiac cycles were averaged. Continuous-wave Doppler was used to measure the aortic transvalvular maximal velocities; the peak and mean gradients were calculated using the simplified Bernoulli equation. The aortic valve area was calculated from the continuity equation.<sup>13</sup>

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Table 1  
Patient characteristics

Variable	No Events (n = 64, 51%)	Events (n = 62, 49%)	Univariate	Multivariate	
			p Value	p Value	Hazard Ratio (95% CI)
Age (years)	68 ± 10	67 ± 12	0.51	—	—
Women	16 (25%)	35 (56%)	0.00024	0.048*	0.53 (0.28–0.99)*
Hypertension	29 (43%)	32 (52%)	0.51	—	—
Diabetes mellitus	12 (19%)	12 (19%)	0.97	—	—
Hypercholesterolemia	28 (44%)	26 (42%)	0.34	—	—
Systolic arterial pressure (mm Hg)	144 ± 18	141 ± 19	0.55	—	—
B-type natriuretic peptide (pg/ml)	39.9 ± 27.3	166 ± 237	<0.0001	0.012*	1.001 (1–1.003)*
Serum creatinine (mg/l)	8.2 ± 1.8	8.7 ± 1.7	0.14	—	—
Abnormal response to exercise	6 (9)	26 (42)	0.007	0.88	0.95 (0.49–1.8)
Aortic valve area (cm <sup>2</sup> )	0.86 ± 0.13	0.79 ± 0.16	0.05	0.80	1.49 (0.06–34)
Peak aortic velocity (m/s)	4.03 ± 0.55	4.35 ± 0.58	0.0013	0.58	1.31 (0.5–3.4)
Aortic peak pressure gradient (mm Hg)	69.7 ± 19.7	77 ± 21	0.01	—	—
Aortic mean pressure gradient (mm Hg)	42.4 ± 13.4	46.7 ± 13.	0.046	0.32	1.02 (0.9–1.06)
Left ventricular mass (g)	174 ± 86	169 ± 67	0.85	—	—
Left ventricular end-diastolic volume (ml)	92.8 ± 26.5	96.9 ± 30.3	0.94	—	—
Left ventricular end-systolic volume (ml)	32.2 ± 14.2	32.5 ± 13	0.91	—	—
Left ventricular ejection fraction (%)	65.8 ± 7.4	67.4 ± 7.5	0.52	—	—
Left atrial area index (cm <sup>2</sup> /m <sup>2</sup> )	10.3 ± 2.1	14.8 ± 3.4	<0.0001	0.011*	1.06 (1.01–1.11)*
Mitral early diastolic filling wave (cm/s)	77 ± 24	83 ± 26	0.12	—	—
Mitral late diastolic filling wave (cm/s)	87 ± 29	89 ± 28	0.29	—	—
Mitral early/late diastolic filling ratio	0.92 ± 0.32	0.99 ± 0.48	0.53	—	—
Mitral early diastolic filling wave deceleration time (ms)	219 ± 78	237 ± 97	0.34	—	—
Peak systolic velocity (cm/s)	5.2 ± 0.9	3.6 ± 1.6	<0.0001	0.016*	0.73 (0.57–0.94)*
Peak early diastolic annular velocity (cm/s)	9.95 ± 1.7	7.9 ± 1.8	0.025	0.91	1.01 (0.84–1.2)
Peak late diastolic annular velocity (cm/s)	8.7 ± 2	7.6 ± 2.1	<0.0001	0.023*	0.81 (0.67–0.97)*
Early diastolic filling/annular velocity (average annuli)	10 ± 3.3	13.5 ± 6.6	0.009	0.024*	0.94 (0.88–0.99)*

\* Parameters selected on the multivariate Cox regression analysis.

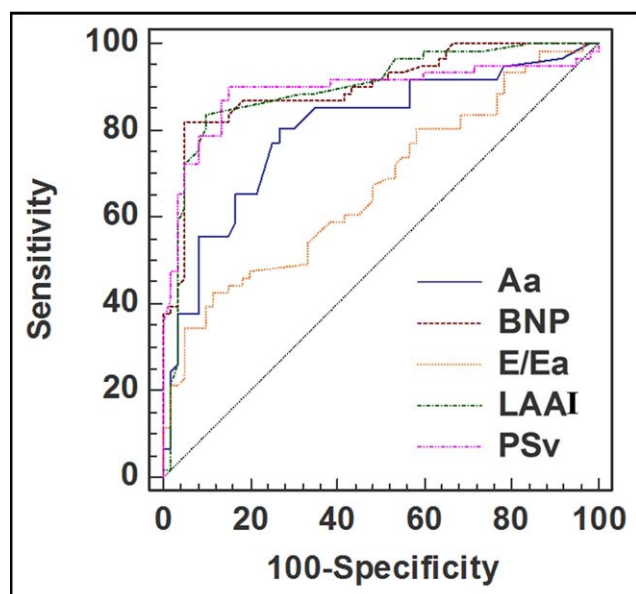


Figure 1. Receiver operating characteristics curves of predictors of outcome. Aa = late diastolic annular velocity; LAAI = left atrial area index; PSv = peak systolic velocity.

The LV end-diastolic and end-systolic volumes and ejection fraction were measured using the bi-apical Simpson disk method.<sup>14</sup> The left atrial area was obtained by planimetry in 2 end-systolic frames of the apical 4-chamber view. Color

Table 2

Area under curve, sensitivity, specificity, and optimal cutoff values of significant variables for predicting outcome

Data at Inclusion	Cutoff Value	Area Under Curve	Sensitivity	Specificity
Left atrial area index (cm <sup>2</sup> /m <sup>2</sup> )	≥12.4	0.90	83.9%	90.6%
Peak systolic velocity (cm/s)	≤4.5	0.87	88.7%	82.8%
Peak Aa velocity (cm/s)	≤9	0.81	80.6%	75%
Early diastolic filling/annular velocity	>13.8	0.67	42%	88%
B-type natriuretic peptide (pg/ml)	≥61	0.89	82%	93.7%

tissue Doppler imaging was performed in the apical views (2 and 4 chamber) to assess longitudinal myocardial function (frame rate ≥115/s).<sup>14</sup> Off-line peak systolic velocities obtained at the level of the septal, lateral, inferior, and anterior mitral annulus were measured separately and then averaged. An effort was made to align each of the LV walls as near to 0° as possible to the long-axis motion. For diastolic function, the peak velocities of early (E) and late (A) diastolic filling, E/A ratio, deceleration time, and isovolumic relaxation time were derived from Doppler recordings of LV inflow. Using pulsed-wave tissue Doppler, the peak velocities during early (Ea) and late (Aa) diastole obtained at the level of the septal and lateral mitral annulus

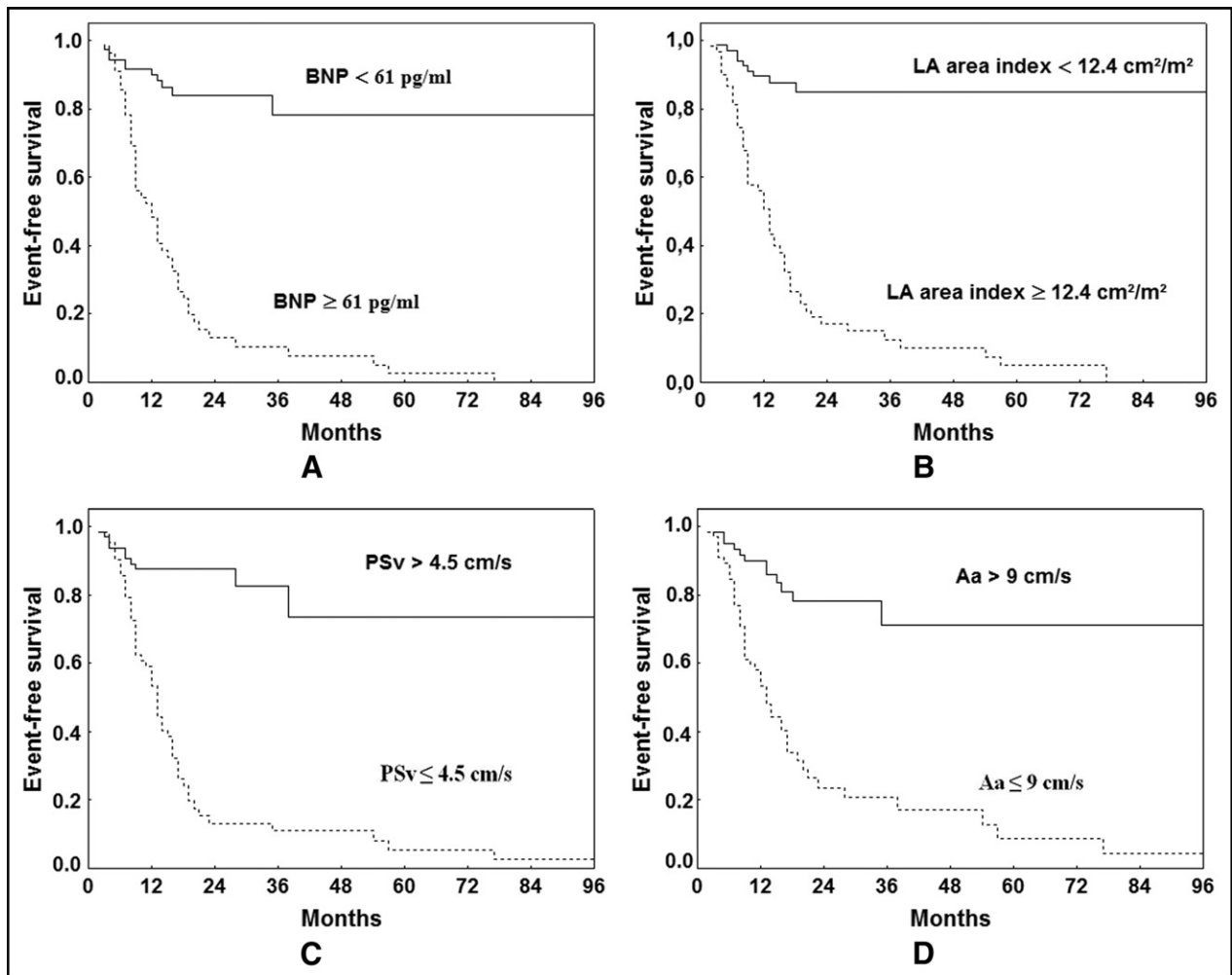


Figure 2. The four figures represent the Kaplan-Meier event-free survival curves according the following categorical variables which were selected in the multivariate model to predict the outcome in asymptomatic patients with AS. (A) BNP: B-Type Natriuretic Peptide; (B) LA: left atrial area; (C) PSv: peak systolic velocity; (D) Aa: late diastolic annular velocity.

were measured separately and then averaged. The E/Ea ratio was then calculated.

Venous blood samples for BNP measurement were drawn before echocardiography, after 10 minutes of supine rest. Chilled ethylenediaminetetraacetic acid tubes were centrifuged immediately at 4,000 rpm (4°C) for 15 minutes. Separated plasma samples were processed by immunofluorescence assay (Biosite, Beckman Coulter, San Diego, California). The inter- and intra-assay variation was 5% and 4%, respectively. The assay detection limit was 1 pg/ml.

Symptom-limited graded bicycle exercise tests were performed at inclusion for all patients. After an initial workload of 25 W maintained for 2 minutes, the load was increased by steps of 25 W every 2 minutes. The exercise test was interrupted when the age-related maximum heart rate was reached or if symptoms, hypotension, or significant ventricular arrhythmias developed. The test was considered abnormal if the patient presented with ≥1 of the following criteria: (1) angina, (2) evidence of dyspnea, (3) dizziness, (4) syncope or near-syncope, (5) and increase in systolic blood pressure during exercise of <20 mm Hg or a decrease in blood pressure, and (6) ventricular tachycardia or >4 pre-

mature ventricular complexes in a row. Because the present study was conducted before the official recommendations of 2007, the results of the exercise test, even when abnormal, did not affect patient treatment.

Follow-up information was obtained from interviews with the patients, their relatives, or their physicians every 6 to 12 months, according to the guidelines. Particular care was taken to obtain information regarding the development of symptoms, eventual aortic valve replacement, and death. The clinical management was determined independently by the patient's personal physician using all information available. The combined end point included the onset of symptoms (angina, dyspnea, syncope, heart failure), cardiac-related death, and the need for aortic valve replacement.

Continuous variables are expressed as the mean ± SD, unless otherwise specified. Group comparisons for categorical variables were obtained using the chi-square test and for continuous variables with 1-way analysis of variance. Analysis was performed by censoring follow-up data at cardiac surgery, if eventually performed. To detect independent predictors of events, a multivariate Cox proportional hazards regression procedure was used to compare the patients

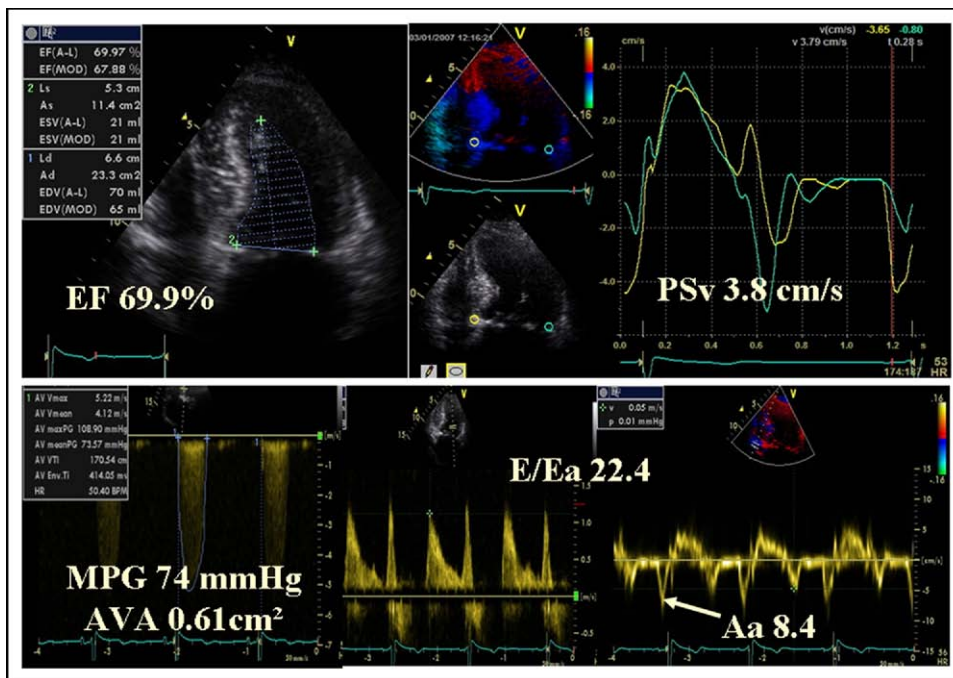


Figure 3. Example of patient with severe AS and impaired long-axis function. Aa = late diastolic annular velocity; AVA = aortic valve area; EF = ejection fraction; MPG = mean transaortic pressure gradient; PSv = peak systolic velocity.

who remained asymptomatic during follow-up and those who experienced an event (STATISTICA, version 7, Statsoft, France). All clinically relevant variables with  $p < 0.10$  were included in the multivariate model.  $p$  Values  $< 0.05$  were considered significant. Receiver operating characteristic curve analysis was performed to determine the cutoff values that best distinguished the issue (area under the curve). Survival curves were established using the Kaplan-Meier method, and statistical significance was determined using the log-rank test.

## Results

The mean patient age was  $67 \pm 10$  years (range 41 to 84). From the patient history and echocardiographic analysis findings, the suspected origin of AS was calcification of a trileaflet ( $n = 104$ ), bicuspid ( $n = 15$ ), rheumatic disease (commissural fusion and calcification most prominent along the edges of the cusps on echocardiography;  $n = 5$ ), and undetermined ( $n = 2$ ). The aortic valve area range was 0.38 to  $1.2 \text{ cm}^2$  (mean  $0.82 \pm 0.15$ ), and the peak aortic pressure gradient was  $77 \pm 21$  mm Hg. The mean aortic pressure gradient was 26 to 86 mm Hg (mean  $45 \pm 14$ ). The mean LV ejection fraction was  $67 \pm 7\%$  (range 55% to 84%), and the mean peak annular systolic velocity was  $4.5 \pm 1.5$  cm/s (range 0.84 to 9). The mean BNP level was  $102 \pm 178$  pg/ml (range 5 to 1,500). At inclusion, the exercise test findings were abnormal (dyspnea in 20, decrease or increase in systolic blood pressure during exercise of  $< 20$  mm Hg in 6, and combined parameters in 6) in 32 patients (25%). During a median follow-up period of  $20.3 \pm 18.7$  months (interquartile range 9 to 22), the predefined end point occurred in 62 patients. Of the 62 patients, 6 patients died from cardiovascular causes: 3 suddenly and 3 from progres-

sive heart failure. Aortic valve replacement was required for the development of symptoms in 34 patients, new-onset atrial fibrillation in 1, newly positive exercise test findings in 7, and equivocal symptoms in 6. Finally, 8 patients developed symptoms but refused to undergo surgery.

The clinical and echocardiographic characteristics of the patients who remained asymptomatic or experienced an event are listed in Table 1. No clinical data, except female gender, allowed the distinction between the 2 groups. Patients who experienced an end point had a smaller aortic valve area, lower tissue Doppler annular systolic and diastolic velocities, and a greater E/Ea ratio, left atrial area, and BNP level. The response to exercise was more often abnormal in these patients. On multivariate Cox regression analysis, the parameters independently associated with the predefined composite outcome were gender, left atrial area index, systolic annular velocity, E/Ea, late diastolic annular velocity (Aa), and BNP level (Figure 1, Table 2). Figure 2 shows the survival curves for categorical variables, and Figure 3 shows an example of a patient with impaired long-axis function. In the subgroup of patients with a normal response to exercise, except for the E/Ea, the other parameters remained independently associated with the outcome.

## Discussion

The decision to perform surgery on asymptomatic patients with AS remains controversial.<sup>3,4</sup> The immediate risks of surgery are often weighed against the later risk of events without intervention.<sup>15</sup> Therefore, reliable risk stratification is clinically important.<sup>16-18</sup> In the present prospective study, we report, for the first time, the added prognostic value of tissue Doppler imaging and BNP measurement compared to

the classical clinical and echocardiographic parameters in a prospective series of patients with asymptomatic moderate to severe AS. Patients, particularly females, with impaired long-axis function and increased BNP levels were at increased risk of untoward events.

In AS, the chronically increased afterload results in progressive LV remodeling and myocardial hypertrophy.<sup>19</sup> Although the increase in LV wall thickness is a compensatory mechanism that reduces systolic wall stress, it can result in impaired LV relaxation, reduced LV compliance, and increased metabolic demands. The ability of the LV to adequately fill under normal pressures is thus altered, and the LV diastolic pressure increases. As a result, LV filling becomes more dependent on the atrial contribution. In the advanced stage of the disease, the chronic increase in LV filling pressure is accompanied by progressive left atrial enlargement and dysfunction.<sup>20</sup> Elevated LV diastolic pressure also limits the coronary perfusion pressure with a reduction of the subendocardial coronary flow reserve, which leads to myocardial ischemia even in the absence of significant coronary artery disease.<sup>21</sup> Despite appropriate hypertrophy and accumulation of collagen in the subendocardial region, the LV ejection fraction can be classically maintained within the normal range for years.<sup>22</sup> This reflects the preserved contribution of radial thickening to LV function. In contrast, the LV longitudinal function will be impaired because of subendocardial dysfunction. Initially, subendocardial dysfunction might normalize after aortic valve surgery.<sup>23</sup>

In the present study, except for female gender, neither the clinical findings (i.e., age, risk factors, exercise test) nor standard echocardiographic parameters (i.e., severity of stenosis, LV mass, LV volume, LV ejection fraction, extent of valve calcification) emerged as independent predictors of outcome. However, the prognostic effect of these factors was probably weakened by the inclusion of almost specifically elderly patients (in which the positive predictive value of exercise testing is limited) and the analysis of more powerful predictors of outcome such as BNP level and tissue Doppler parameters.<sup>24,25</sup> In these patients, the increased release of BNP from the ventricles could reflect the substantial gender differences in the LV adaptive responses to AS.<sup>26</sup> BNP has been shown to be associated with the prognosis in several cardiovascular diseases such as AS.<sup>7-11</sup> In heart failure, the predictive value of BNP seems to be greater in women than in men.<sup>27</sup> Our results have confirmed the strong prognostic value of BNP in a cohort of patients with asymptomatic AS.

The current guidelines consider surgery as reasonable in patients with asymptomatic severe AS and reduced LV ejection fraction (<50%).<sup>3,4</sup> However, the LV ejection fraction is often normal in these patients. In contrast to this crude estimate of the LV systolic function, tissue Doppler imaging is superior for detecting subtle changes in myocardial function.<sup>12</sup> Measurements of myocardial systolic annular velocities reflect longitudinal motion owing to the longitudinally directed fibers, which are mainly located in the subendocardium and subepicardium. When the velocities are averaged from the 4 regions of the annulus, they reflect the global long-axis function. In patients with asymptomatic AS, impaired subendocardial function has been shown to be

associated with impaired exercise tolerance and changes in symptomatic status during short-term follow-up.<sup>6,22</sup> Our results have extended these preliminary data by showing that the decrease in long-axis function can identify a subset of patients with moderate to severe asymptomatic AS at greater risk of developing cardiac events.

In the present study, we found that the left atrial area, late diastolic annular velocity (Aa), and E/Ea ratio were strong independent predictors of outcome. The left atrial size reflects the chronicity of diastolic burden.<sup>28</sup> A value of  $\geq 12.4$  cm<sup>2</sup>/m<sup>2</sup> provided high predictive accuracy for cardiac events. The late diastolic annular velocity reliably quantifies the left atrial contribution to LV filling. In these patients, the left atrial booster pump function has a crucial role in counteracting the increased LV end-diastolic pressure and the delayed LV untwisting to maintain optimal cardiac output.<sup>29</sup> A reduction in left atrial function might thus favor clinical deterioration. In our population, a late diastolic annular velocity of  $\leq 9$  cm/s was associated with an excess risk of death, symptoms, or surgery. An increased E/Ea ratio, an estimate of LV pre-A pressure, has been shown to be an important marker of adverse events in patients with preserved LV function.<sup>12</sup> In the present study, we found that an E/Ea ratio  $> 13.8$  identified a subset of patients with AS at greater risk of future events.

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