**B-Type Natriuretic Peptide Clinical Activation in Aortic Stenosis**

Impact on Long-Term Survival

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**Objectives**

This study was conducted to define the association between serum B-type natriuretic peptide (BNP) activation and survival after the diagnosis of aortic stenosis (AS).

**Background**

In AS, the link between BNP levels and clinical outcome is in dispute. Failure to account for the normal shifting of BNP ranges with aging in men and women, not using hard endpoints (survival), and not enrolling large series of patients have contributed to the uncertainty.

**Methods**

A program of prospective measurement of BNP levels with Doppler echocardiographic AS assessment during the same episode of care was conducted. BNP ratio (measured BNP/maximal normal BNP value specific to age and sex) >1 defined BNP clinical activation.

**Results**

In 1,953 consecutive patients with at least moderate AS (aortic valve area 1.03 ± 0.26 cm²; mean gradient 36 ± 19 mm Hg), median BNP level was 252 pg/ml (interquartile range: 98 to 592 pg/ml); BNP ratio 2.46 (interquartile range 1.03 to 5.66); ejection fraction (EF) 57% ± 15%, and symptoms present in 60% of patients. After adjustment for all survival determinants, BNP clinical activation (BNP ratio >1) independently predicted mortality after diagnosis (p < 0.0001; hazard ratio [HR]: 1.91; 95% CI: 1.55 to 2.35) and provided incremental power to the survival predictive model (p < 0.0001). Eight-year survival was 62 ± 3% with normal BNP levels, 44 ± 3% with BNP ratio of 1 to 2 (adjusted HR: 1.49; 95% CI: 1.17 to 1.90), 25 ± 4% with BNP ratio of 2 to 3 (adjusted HR: 2.12; 95% CI: 1.63 to 2.75), and 15 ± 2% with BNP ratio of ≥3 (adjusted HR: 2.43; 95% CI: 1.94 to 3.05). This strong link to survival was confirmed in asymptomatic patients with normal EF (adjusted HR: 2.35 [95% CI: 1.57 to 3.56] for BNP clinical activation and 2.10 [95% CI: 1.32 to 3.36] for BNP ratio of 1 to 2, 2.25 [95% CI: 1.31 to 3.87] for BNP ratio of 2 to 3, 3.93 [95% CI: 2.40 to 6.43] for BNP ratio of ≥3). Aortic valve replacement was associated with survival improved by a similarly high margin (p = 0.54 with BNP ratio of <2 [HR: 0.68; 95% CI: 0.52 to 0.89; p = 0.003] or BNP ratio of ≥2 [HR: 0.56; 95% CI: 0.47 to 0.66; p < 0.0001]).

**Conclusions**

In this large series of patients with AS, BNP clinical activation was associated with excess long-term mortality incrementally and independently of all baseline characteristics. Higher mortality with higher BNP clinical activation, even in asymptomatic patients, emphasizes the importance of appropriate clinical interpretation of BNP levels in managing patients with AS. (J Am Coll Cardiol 2014;63:2016–25) © 2014 by the American College of Cardiology Foundation

Plasma levels of B-type natriuretic peptide (BNP) have been shown to be predictive of outcome and to be clinically useful in diagnosis, management, and risk stratification of cardiovascular diseases such as heart failure and acute coronary syndromes (1–4). In aortic stenosis (AS), pilot studies have suggested that BNP levels may be related to disease severity, symptoms, and mixed measures of outcome (5–10), but a recent prospective analysis raised a concern that these presumptive outcome implications may have been...
overemphasized (11). Survival association with BNP levels was analyzed in very small sets of mostly symptomatic patients (9,12,13) and thus remains undefined. Another source of uncertainty is that these pilot studies used different assays and forms of BNP that are not well harmonized (6–9). Considerably different absolute thresholds proposed in these studies to stratify risk may reflect low power in small, variably selected patient populations with short follow-up or may reflect the instability of soft outcome endpoints (aortic valve replacement, symptom onset, or combined endpoint of variable cardiac events). Furthermore, normal values of BNP for age and sex were not taken into account to affirm BNP clinical activation in excess of the normal range. Thus, the use of BNP as a marker of AS outcome has not been adequately validated for use in clinical practice and is not recommended in guidelines (14,15).

Obtaining objective markers of outcome is crucial in AS. Indeed, AS is frequent (16) and is the most common valvular disease referred for valve replacement (17), which is the only effective AS treatment (14,15), including transcutaneous insertion (15). The role of symptom onset has been emphasized (18,19), but epidemiologically changes, with the current predominance of degenerative AS, are characterized by elderly patients being predominantly affected and in whom evaluation and interpretation of symptoms is challenging (20). Therefore, objective markers of risk are crucial in that environment; as such, BNP could play an essential role in risk stratification. For that purpose, it is essential to account for the shifting normal BNP range with aging and specific to each sex and to assess a hard endpoint, particularly mortality, requiring a large cohort of patients diagnosed with AS.

Thus, the objectives of our study were to assess the link between BNP values measured at diagnosis, particularly BNP clinical activation (accounting for the normal BNP range specific to each patient) and mortality following the diagnosis of moderate or severe AS, and to examine the hypothesis that BNP clinical activation independently predicts excess mortality after adjustment for all baseline characteristics, even in asymptomatic patients. A secondary hypothesis examined was that higher levels of activation are associated with more severe outcomes.

**Methods**

Following a pilot study of natriuretic peptides in valvular heart diseases (21,22), we initiated a program of prospective and systematic measurement of BNP levels with comprehensive Doppler echocardiographic evaluation of valve diseases performed during the same episode of care. For the purpose of the present study, we gathered 1,953 consecutive patients who were diagnosed with moderate or severe AS based on aortic valve area (AVA) of <1.5 cm² by Doppler echocardiography and who underwent this combined clinical, hormonal, and Doppler echocardiographic assessment. Patients with known rheumatic valve disease (clinically and/ or echocardiographically); congenital heart disease (except overt or unknown bicuspid valve or patent foramen ovale); previous valvular surgery; acute myocardial infarction within 8 weeks preceding AS diagnosis; atrial fibrillation with rapid ventricular response; history or current endocarditis; pericarditis with or without tamponade; sepsis; severe liver, kidney, or brain disease except old stroke; hyperparathyroidism; or Cushing disease were excluded. Non-U.S. citizens were excluded to ensure homogeneous Social Security death data. The study was approved by our institutional review board.

**Clinical data.** Clinical data were collected by the patients’ personal physicians during the same episode of care as the Doppler echocardiographic and hormonal assessment. The Charlson score index was calculated as previously published (23). Symptomatic patients presented with syncope or near syncope, dyspnea, and/or probable or classic angina.

**Doppler echocardiography.** All patients underwent comprehensive Doppler echocardiography using standard ultrasound systems, including interrogation from all possible windows (24). All measurements and calculations were performed as recommended by echocardiographic societies’ recommendations (25). After measurement in systole of aortic annulus diameter, flow velocity and time velocity integral of left ventricular outflow tract by pulsed-wave Doppler, and AS jet by continuous-wave Doppler, we measured peak jet velocity and mean gradient and calculated AVA by continuity equation as an absolute value and indexed to body surface area. AS severity was graded according to current guidelines (14) and recent community studies (20) as moderate AS with AVA of 1.0 to 1.5 cm² or severe AS with AVA of ≤1.0 cm².

**Laboratory data.** Venous blood samples were drawn from an antecubital vein into chilled ethylenediaminetetraacetic acid Vacutainer test tubes (Becton, Dickinson and Company, Franklin Lakes, New Jersey). Plasma separation was immediately performed at −4°C, and plasma samples were frozen at −70°C until assay. Plasma BNP levels were determined by immunoenzymatic assay (Triage, Biosite Inc., San Diego, California) within 3 days. The ratio between measured serum BNP level and maximal normal BNP level for age and sex (BNP ratio) was calculated for each patient (26). The maximal normal values of BNP specific to age and sex were derived from Mayo Clinic laboratory procedures. Patients with elevated BNP levels (i.e., BNP ratio >1) were considered as displaying BNP clinical activation.

**Endpoints.** The primary endpoint of this study was the overall mortality after diagnosis, and the secondary endpoint was mortality under medical treatment. This secondary endpoint was assessed in the whole cohort with censoring at the time of aortic valve replacement (AVR) if performed. Due to the large size of our series, we elected to follow up
on patients using electronic records of events from internal computerized databases and from the Social Security Death Index. For maximizing interrogation of the central Social Security Death Index database, a multiple demographic list (such as first and last name, date of birth, and Social Security number) and a delay of 1 year between interrogation and closing follow-up date were used (27,28).

**Statistical analysis.** Results are expressed as mean ± SD, median with interquartile range, or percentage when appropriate. Continuous variables were tested for distribution normality with the Shapiro-Wilk test. Because BNP absolute values and BNP ratio were not normally distributed, natural log transformations of BNP and BNP ratio were used for BNP continuous variable analyses (unless otherwise specified). BNP ratio was also categorically analyzed. Analysis of survival used patients with normal BNP levels as reference compared with those with BNP clinical activation overall or stratified into 3 groups (1 to 2, 2 to 3, or ≥3), or quintiles of elevated BNP ratio distribution.

Univariable and multivariable models used Cox proportional hazards for survival analysis. To analyze BNP incremental value, we defined a background model to predict mortality including age, sex, body surface area, atrial fibrillation, Charlson score index, symptoms, creatinine level, hemoglobin level, systolic blood pressure, indexed AVA, and left ventricular ejection fraction (LVEF). All variables in the Cox models verified the proportional hazards assumption on the basis of inspection of trends in the Schoenfeld residuals (all p > 0.15). AVR was used as a time-dependent covariate in the multivariable Cox proportional hazards models. The time between diagnosis and AVR was considered as medical treatment follow-up. Using age, sex, creatinine level, hemoglobin level, LVEF, mean gradient, indexed AVA, atrial fibrillation, systolic blood pressure, body surface area, coronary artery disease, previous myocardial infarction, hypertension, previous open heart surgery, diabetes, renal disease, and symptoms, we calculated case–weight estimation with a logistic regression model to predict the inverse probability of having an AVR. With this inverse probability of treatment weighting, baseline characteristics were compared between patients with and without AVR during follow-up with the use of weighted Student t test or weighted Wilcoxon rank-sum test for continuous variables and weighted chi-square test or Fisher exact test for categorical variables, as appropriate. Inverse probability–weighted Cox multivariable models were used to analyze potential impact of AVR overall and stratified by BNP ratio <2 or ≥2.

BNP additional impact on survival after diagnosis was analyzed by adding BNP (expressed as a continuous or categorical variable) to the background survival model and assessing model incremental power using the likelihood ratio test. Survival models are presented with BNP hazard ratio (HR) and 95% CI.

A p value <0.05 was considered statistically significant. Statistical analyses were performed with JMP 9.1 and SPSS 20.0 software.

### Results

#### Baseline characteristics

The baseline characteristics of the entire cohort are presented in Table 1, left column. Consistent with typical characteristics of patients diagnosed with moderate to severe AS, age was 76 ± 12 years and 1081 (55%) patients were male. With LVEF of 57 ± 15%, the AS characteristics were coherent with AVA was 1.03 ± 0.26 cm², mean gradient 36 ± 19 mm Hg and peak velocity 3.78 ± 0.95 m/s. In term of comorbidity, prevalence of hypertension (70%), atrial fibrillation (20%), diabetes (30%), chronic pulmonary disease (32%), and chronic kidney disease (36%) were as expected in a population of that age. Median (interquartile range) of BNP was 252 (98 to 592) pg/ml and that of BNP ratio was 2.46 (1.03 to 5.66), with BNP clinical activation noted 2.46 (1.03 to 5.66), with BNP clinical activation noted 2.46 (1.03 to 5.66), with BNP clinical activation noted 2.46 (1.03 to 5.66), with BNP clinical activation noted 2.46 (1.03 to 5.66), with BNP clinical activation noted 2.46 (1.03 to 5.66).
11.6% to 2, and 43.8% >3). The distribution in quintiles of patients with BNP ratio >1 corresponds to thresholds of BNP ratio of 1.71, 2.87, 4.78, and 9.28. Among the 1,953 patients, 565 (29%) were asymptomatic with preserved LVEF (i.e., >50%) and no history of myocardial infarction (Table 1).

Clinical activation of BNP and overall survival in the whole cohort. During a mean follow-up of 3.8 ± 2.4 years, there were 828 AVRs (1,125 patients had only follow-up under medical management) and 1,070 deaths. Overall survival at 2, 5, and 8 years was 73% ± 1%, 49% ± 1%, and 34% ± 2%. In univariable analysis, expressed as continuous variables, ln BNP and ln BNP ratio were associated with increased overall mortality (HR: 1.68 [95% CI: 1.60 to 1.77; p < 0.0001] and HR: 1.54 [95% CI: 1.47 to 1.62; p < 0.0001], respectively). After adjustment for the background model, ln BNP (HR: 1.40; 95% CI: 1.31 to 1.50; p < 0.0001) or ln BNP ratio (HR: 1.40; 95% CI: 1.31 to 1.50; p < 0.0001) was an independent predictor of mortality after diagnosis. BNP clinical activation as a categorical variable was independently associated with excess mortality (HR: 1.91; 95% CI: 1.55 to 2.35; p < 0.0001). The addition of BNP clinical activation (or the BNP ratio as continuous variable) to the background comprehensive model of survival determinants, showed that BNP considerably increased model predictive power (p < 0.0001) (Table 2). Moreover, with a higher degree of BNP clinical activation, excess mortality increased markedly. Indeed, analyzed as quintiles of activated BNP, each quintile of abnormal BNP ratio was associated with excess mortality versus normal BNP reference group (Fig. 1A) but also showed 40% to 60% additional risk of mortality compared with each previous quintile of abnormal BNP ratio (all p ≤ 0.004) (Fig. 2A). Furthermore, upon examination of specific thresholds of BNP clinical activation (Table 2), all activated subgroups incurred excess mortality, but the risk increased from BNP ratio 1 to 2 to 3 to >3 (Figs. 1B and 2B). The adjusted HRs of 1.49 to 2.12 to 2.43 signified that, compared with patients with BNP ratio within the normal range, those with elevated BNP ratio lower than twice normal had a 49% increased mortality risk independent of other baseline characteristics, those with elevated BNP ratio 2 to 3 times normal had 112% increased mortality risk, and those with BNP ratio higher than 3 times normal had 143% increased mortality risk (Table 2 and Fig. 1B). Survival 8 years after diagnosis was 62 ± 3% in patients with BNP ratio within normal range versus 24 ± 2% for those with BNP clinical activation (p < 0.0001), and survival decreased proportionately with higher thresholds of BNP activation (Fig. 3A). In estimating the therapeutic effect of AVR, the inverse probability weight was effective at abolishing the differences in baseline characteristics between patients who underwent an AVR during follow-up and those who did not. Within that process, after adjusting for baseline characteristics, we found that the HR estimate of AVR benefit (time dependent) was similar in patients with BNP ratio ≥2 and those with BNP ratio <2 (HR: 0.56 [95% CI: 0.47 to 0.66] vs. HR: 0.68 [95% CI: 0.52 to 0.88]; p = 0.54) (Fig. 4), demonstrating that the mortality increase in those with markedly elevated BNP ratio was similarly palliated by AVR and thus in all likelihood is indeed related to AS.

Survival under medical management. When survival under medical management was analyzed, the results were similar. During a mean follow-up of 2.1 ± 2.2 years under medical management, there were 791 deaths. Overall survival under medical management at 2, 5, and 8 years was 68 ± 1%, 38 ± 2%, and 21 ± 2%. As continuous variables, adjusted for the background model, ln BNP (HR: 1.41; 95% CI: 1.30 to 1.54; p < 0.0001) or ln BNP ratio (HR: 1.41; 1.30–1.54; p < 0.0001) was independently predictive of mortality (Table 2). BNP clinical activation was associated with a similarly increased mortality under medical management (as overall survival), with adjusted HR of 1.84 (95% CI: 1.44 to 2.35; p < 0.0001), and the addition of BNP ratio to the model markedly increased its predictive power (p < 0.0001). Survival under medical management 8 years after diagnosis was 49 ± 5% in patients without BNP clinical activation versus 13 ± 2% for those with BNP clinical activation (p < 0.0001). Strata of clinical activation of BNP manifested the same trend for higher mortality risk with medical treatment when higher levels of BNP clinical activation were present (Table 2).

Survival of isolated AS. Patients with isolated AS were asymptomatic, had no history of myocardial infarction, and had normal LVEF at diagnosis. For these 565 patients with isolated AS, baseline characteristics were more favorable than those of the entire series (Table 1), but the results in terms of link between BNP clinical activation and mortality were similar to those observed in the entire series. During a mean follow-up of 4.3 ± 2.4 years, there were 265 AVRs and 227 deaths and overall survival at 2, 5, and 8 years was 80 ± 2%, 62 ± 2%, and 54 ± 3%. In BNP and ln BNP ratio were independent predictors of mortality (both p < 0.0001) (Table 2). BNP clinical activation was independently associated with excess mortality (adjusted HR: 2.35; 95% CI: 1.57 to 3.56; p < 0.0001), and addition of BNP clinical activation to the survival model markedly increased its predictive power (p < 0.0001). The survival of isolated AS 8 years after diagnosis was 75 ± 4% without versus 38 ± 4% with BNP clinical activation (p < 0.0001). Survival after diagnosis in the 4 defined strata of BNP clinical activation shown in Figure 3B demonstrates widely divergent survival rates. Adjusted in comprehensive multivariable models, the degree of BNP clinical activation was highly and progressively associated with survival, as shown in Table 2 (right column), with mortality risk approximately doubled versus normal BNP with BNP ratio of 1 to 2, whereas the risk of death approximately quadrupled with BNP ratio ≥3 (Table 2). When this analysis was restricted to severe AS (mean gradient >40 mm Hg, peak aortic jet velocity >4 m/s, or AVA <1.0 cm²), the excess mortality
associated with degrees of BNP clinical activation was confirmed and impressive (adjusted HR: 3.02 [95% CI: 1.31 to 6.93] for BNP ratio 1 to 2, 4.64 [95% CI: 1.99 to 10.81] for BNP ratio 2 to 3, and 7.38 [95% CI: 3.27 to 16.66] for BNP ratio ≥3; all p < 0.01).

**Discussion**

The present study analyzing the association of BNP at diagnosis with survival after diagnosis of moderate or severe AS has unique methodological characteristics, emphasizing...
its significance. First, BNP measurement was integrated into a clinical program, explaining the unique similarity between AS characteristics in our series and in the community. BNP expression accounting for shifting normal ranges of BNP level with age and sex can thus be individualized to each patient. The large power of the series allows ascertaining the independent and incremental link between BNP and survival. Major findings of our study were the additional prognostic value provided by BNP ratio in patients diagnosed with AS and the association of BNP clinical activation with excess mortality overall, under medical management, and in isolated AS (no symptoms or myocardial infarction and normal EF). Another major finding is that BNP is a quantitative marker of outcome, whereby higher degree of BNP clinical activation predicts higher long-term mortality in all subsets of patients with AS. The fact that AVR is independently associated with markedly improved prognosis in patients with clinically activated BNP strongly suggests that AS and BNP values are linked and that BNP clinical activation should be taken into account in the clinical
BNP measure to be usable in clinical practice, it is essential within the normal range for older patients. Thus, for the surrogates for the known BNP-age link (26) and may fall with heart failure (30) so that interpreting absolute BNP with valvular diseases is tempting, pilot studies have shown linked to outcome in pilot studies (7,21,33,34) may just be valvular diseases, the low and widely discrepant thresholds (31,32), may be disputable for valve diseases. Indeed, in levels, which is appropriate for heart failure management percutaneous AVR (15,36). Symptoms have been considered as a prognostic marker in a range of conditions and has been extensively validated in heart failure and acute coronary syndromes (1–4). Although emulating similar approaches with valvular diseases is tempting, pilot studies have shown that BNP levels are much lower with valvular disease than with heart failure (30) so that interpreting absolute BNP levels, which is appropriate for heart failure management (31,32), may be disputable for valve diseases. Indeed, in valvular diseases, the low and widely discrepant thresholds linked to outcome in pilot studies (7,21,33,34) may just be surrogates for the known BNP-age link (26) and may fall within the normal range for older patients. Thus, for the BNP measure to be usable in clinical practice, it is essential for the specific BNP assay used (35) and the patient’s individual normal BNP range, such as by using the BNP ratio, are recorded. This approach has the advantage of detecting a graded response in relation to outcomes and to affirm the generally benign survival of patients with valve diseases and BNP values within the normal range.

**BNP as predictor of outcome in AS.** AS is frequent (16), and its prognosis is considerably improved by surgical or percutaneous AVR (15,36). Symptoms have been considered main determinants of survival (18) and main triggers for AVR (14,15) However, with aging of the population and increasing predominance of degenerative AS (16), diagnosis made mostly occurs in the mid-seventh decade (20) so that symptoms (of any cause including deconditioning) or markedly reduced activity are frequent (20). Frequent comorbidities may also cause symptoms similar to those of AS. Hence, clinical manifestations can be quite challenging to interpret, and objective markers of outcome are crucial in stratifying risk at diagnosis. For this purpose, BNP level may play an important role if its link to survival is ascertained. Previous studies were small with soft endpoints and were discordant in term of mere prognostic value (11) and in term of usable thresholds (7–9,34) but were hypothesis generating for the present study.

Our study, with close to 2,000 consecutive patients and comprehensive baseline clinical and Doppler echocardiographic data measured during the same episode of care, provides ample power to analyze survival after diagnosis and demonstrate the incremental prognostic value of BNP level over classical outcome predictors (9). BNP clinical activation, our main BNP characterization, with levels higher than normal, individualized for each patient, independently predicted survival, incrementally to all other baseline predictors, even accounting for AVR performance. Furthermore, BNP is a quantitative determinant of survival, whereby higher BNP ratio levels, representing more intense BNP clinical activation, indicates higher mortality risk after diagnosis. This quantitative pattern and predictive value of BNP ratio is also observed in patients without obvious other contributors to BNP clinical activation, specifically those with no symptoms, no overt LV dysfunction, and no history of myocardial infarction. It remains highly pertinent when restricted to patients with severe AS only. Thus, it is likely that a direct link between BNP levels and AS, rather than an extraneous cause, is key to BNP outcome impact. This link may be debated (11), but it is further supported by considerable survival improvement after AVR in those with notable BNP clinical activation (BNP ratio >2).

The specific subset of patients with asymptomatic AS, normal EF, and no previous myocardial infarction is of great interest. Initial reports suggested that outcomes were

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**Table 2** Hazard Ratios, 95% CI, and p Values for Different Variables and Thresholds of BNP

<table>
<thead>
<tr>
<th>Variable</th>
<th>Overall Mortality Univariate Analysis</th>
<th>Overall Mortality Whole Cohort</th>
<th>Mortality Under Medical Treatment Whole Cohort</th>
<th>Overall Mortality Asymptomatic Isolated AS</th>
</tr>
</thead>
<tbody>
<tr>
<td>In BNP</td>
<td>HR (95% CI)</td>
<td>1.68 (1.60–1.77)</td>
<td>1.40 (1.31–1.50)</td>
<td>1.41 (1.30–1.54)</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>In BNP ratio</td>
<td>HR (95% CI)</td>
<td>1.54 (1.47–1.62)</td>
<td>1.40 (1.31–1.50)</td>
<td>1.41 (1.30–1.54)</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Activated BNP &lt; 1 times normal</td>
<td>HR (95% CI)</td>
<td>3.08 (2.59–3.69)</td>
<td>1.91 (1.55–2.35)</td>
<td>1.84 (1.44–2.35)</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
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</tr>
<tr>
<td>Activated BNP &lt; 2 times normal</td>
<td>HR (95% CI)</td>
<td>1.80 (1.44–2.25)</td>
<td>1.49 (1.17–1.90)</td>
<td>1.43 (1.08–1.90)</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td>0.001</td>
<td>0.008</td>
</tr>
<tr>
<td>Activated BNP &lt; 3 times normal</td>
<td>HR (95% CI)</td>
<td>3.13 (2.48–3.96)</td>
<td>2.12 (1.63–2.75)</td>
<td>2.10 (1.55–2.86)</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
<tr>
<td>Activated BNP ≥ 3 times normal</td>
<td>HR (95% CI)</td>
<td>4.06 (3.38–4.91)</td>
<td>2.43 (1.94–3.05)</td>
<td>2.21 (1.69–2.88)</td>
</tr>
<tr>
<td>p Value</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

* Adjusted for age, sex, body surface area, atrial fibrillation, Charlson score index, symptoms, creatinine level, hemoglobin level, systolic blood pressure, indexed aortic valve area, indexed stroke volume, and LV ejection fraction. ** Further adjustment for aortic valve replacement as a time-dependent variable. † Asymptomatic Isolated AS group was defined as asymptomatic AS with normal ejection fraction and no previous myocardial infarction. | Compared with normal BNP level. 

Abbreviations as in Table 1.
favorable (37,38), particularly in young patients (39). However, recent reports have indicated notable sudden death rates, even in patients truly symptom free (40) and excess mortality occurring over time (40,41) confirmed in the community, ruling out aberrations due to referral bias or excess comorbidity (20). Thus, it is likely that patients with AS, asymptomatic and with EF >50%, are heterogeneous, some indeed with benign outcome but others with moderate (40) or even high (41) risk that we are currently poorly equipped to define (14,15). Although exercise testing may contribute to decision making (42,43), it may be of limited use in an elderly population, and BNP has a critical role to play in this subset (6,7). Indeed, we observed that in asymptomatic patients with AS, normal EF, and no history of myocardial infarction, BNP activation is not only independently and incrementally predictive of survival after diagnosis but also activation magnitude is crucially important in defining prognosis. Because BNP levels have been correlated to myocardial fibrosis and its surrogate markers (44–47), BNP clinical activation may indicate, with a simple blood test, ongoing ventricular alterations that may ultimately impact survival. Hence, we believe that detection of BNP clinical activation represents a useful goal in clinical practice for management of patients with AS, even asymptomatic, as an incremental risk marker. No single prognostic marker should be taken as an absolute decision maker. Physicians should integrate all possible patient descriptors, including age, comorbidity, frailty, AS severity and
consequences, and patient desires into each clinical decision. Our data clearly showed that BNP activation should be one of the elements that participate in this comprehensive assessment of patients with AS.

**Study limitations.** Our design, routine clinical practice cohort with hormonal levels, clinical, and Doppler echocardiographic data collected prospectively, but with no mandate to arrange follow-up with investigators, maintained the central role of the personal physician. The disadvantage of this design is that strict plans of care by investigators cannot be enforced; therefore, ultimate decisions are made by patients and personal physicians. The notable advantage of this design is the large number of patients participating, demonstrating unique statistical power, and the limited enrollment bias demonstrated by the similarity of the current enrolled population with patients diagnosed with AS in the community (20). We did not evaluate serial values of BNP; however, now that the link of BNP to survival has been established, future studies with serial measurements may demonstrate additional prognostic power.

We could not secure funding to perform systematic multiple testing simultaneously, such as computed tomography, magnetic resonance imaging, and measurement of multiple blood markers simultaneously to calculate BNP levels. We also did not measure NT-pro-BNP to compare predictive values of these 2 assays, which may not be equivalent prognostically in valve diseases, potentially explaining discordances in the literature (11). We believe that future mechanistic studies should be conducted in that regard, now that the present series has demonstrated the critical role of BNP as a marker of survival after AS diagnosis. Comorbidities may influence BNP activation but were accounted for by exclusion criteria, by adjusting for specific baseline characteristics, and by analysis of subsets when there was no other identified cause of BNP activation. Mild kidney or liver disease or atrial fibrillation with controlled heart rate were included but did not affect the BNP-survival link. Despite our large sample size and event numbers, power was not sufficient to analyze all possible subgroups in multiple comparisons and should be addressed by future large collaborative studies. Our study raises the question of potential benefit of AVR in AS with elevated BNP levels for which a randomized control trial would be warranted.

**Conclusions**

In this large cohort of patients with moderate or severe AS, BNP clinical activation, defined as levels higher than the upper limit of normal for each individual patient, was a powerful predictor of long-term mortality, incrementally and independently of all baseline characteristics. Moreover BNP was a quantitative marker of outcome, whereby higher activation predicted higher mortality, and was particularly effective in the important subset of asymptomatic patients with normal EF and no history of myocardial infarction. Thus, BNP measurement and BNP ratio calculation should be included for risk stratification in clinical practice and for consideration of AVR, which is associated with considerable reduction of mortality, even in patients with marked BNP clinical activation.

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**REFERENCES**

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