B-Type Natriuretic Peptide in Low-Flow, Low-Gradient Aortic Stenosis
Relationship to Hemodynamics and Clinical Outcome: Results From the Multicenter Truly or Pseudo-Severe Aortic Stenosis (TOPAS) Study

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**Background**—The prognostic value of B-type natriuretic peptide (BNP) is unknown in low-flow, low-gradient aortic stenosis (AS). We sought to evaluate the relationship between AS and rest, stress hemodynamics, and clinical outcome.

**Methods and Results**—BNP was measured in 69 patients with low-flow AS (indexed effective orifice area <0.6 cm$^2$/m$^2$, mean gradient ≤40 mm Hg, left ventricular ejection fraction ≤40%). All patients underwent dobutamine stress echocardiography and were classified as truly severe or pseudosevere AS by their projected effective orifice area at normal flow rate of 250 mL/s (effective orifice area ≤1.0 cm$^2$ or >1.0 cm$^2$). BNP was inversely related to ejection fraction at rest (Spearman correlation coefficient $r_s = -0.59$, $P<0.0001$) and at peak stress ($r_s = -0.51$, $P<0.0001$), effective orifice area at rest ($r_s = -0.50$, $P<0.0001$) and at peak stress ($r_s = -0.46$, $P=0.0002$), and mean transvalvular flow ($r_s = -0.31$, $P=0.01$). BNP was directly related to valvular resistance ($r_s = 0.42$, $P=0.0006$) and wall motion score index ($r_s = 0.36$, $P=0.004$). BNP was higher in 29 patients with truly severe AS versus 40 with pseudosevere AS (median, 743 pg/mL [Q1, 471; Q3, 1356] versus 394 pg/mL [Q1, 191 to Q3, 906], $P=0.012$). BNP was a strong predictor of outcome. In the total cohort, cumulative 1-year survival of patients with BNP ≥550 pg/mL was only 47±9% versus 97±3% with BNP <550 (P<0.0001). In 29 patients who underwent valve replacement, postoperative 1-year survival was also markedly lower in patients with BNP ≥550 pg/mL (53±13% versus 92±7%).

**Conclusions**—BNP is significantly higher in truly severe than pseudosevere low-gradient AS and predicts survival of the whole cohort and in patients undergoing valve replacement. *(Circulation. 2007;115:2848-2855.)*

**Key Words:** aorta • echocardiography • natriuretic peptides • prognosis • survival • valves

**Editorial p 2799**

**Clinical Perspective p 2855**

Plasma levels of B-type natriuretic peptide (BNP) have recently been shown to relate to AS severity and predict symptoms, survival, and postoperative outcome.
40 mm Hg, and LV ejection fraction (EF) has previously been described in detail. Prospective study has been performed at rest and under dobutamine stress as reported in detail. Cardiac output was determined by multiplication of the heart rate by the stroke volume, derived in the LV outflow tract (LVOT) from the product of the LVOT velocity-time integral and cross-sectional area. Cine loops of apical 4- and 2-chamber, parasternal long-axis, and short-axis views were obtained and the LVEF and wall motion score index were measured off-line. The LVEF was determined by the Simpson method. The wall motion score index was derived by addition of the wall motion score of each of the 16 myocardial segments (0, normal; 1, hypokinetic; 2, akinetic; 3, dyskinetic) and division by the number of visualized segments.

However, no data have been reported for the subset of patients with low-flow, low-gradient AS. Therefore, we sought to evaluate the relationship between BNP and the hemodynamic and clinical variables at study entry in patients with low-flow, low-gradient AS enrolled in the Truly or Pseudo-Severe Aortic Stenosis (TOPAS) multicenter study and whether BNP would be useful to separate patients with TS AS from those with PS AS. More important, we studied whether BNP is a predictor of outcome and may therefore aid in clinical decision making for surgical versus medical treatment in these challenging patients.

### Methods

#### Patients and Study Protocol

The design of the TOPAS multicenter (Quebec Heart Institute, University of Ottawa Heart Institute, and Vienna General Hospital) prospective study has previously been described in detail. Patients with AS were included when the effective orifice area (EOA) was ≤1.2 cm², the indexed EOA ≤0.6 cm²/m², mean gradient ≤40 mm Hg, and LV ejection fraction (EF) ≤40% on Doppler-echocardiographic examination. Exclusion criteria were aortic regurgitation >2+, mitral valve disease with valve area <2.0 cm² or regurgitation >2+ caused by intrinsic valve pathology, atrial fibrillation, paced rhythm, unstable angina, acute pulmonary edema, pregnancy or lactation, and end-stage renal disease. In addition, patients with plasma creatinine >3 mg/dL were excluded in the BNP substudy.

The study was approved by the local ethics committees and patients gave written informed consent. From July 2002 to November 2005, 69 patients with low-flow, low-gradient AS were recruited in the study. Baseline characteristics of all patients are shown in Table 1.

As described previously, all patients underwent a medical history and physical examination. Coronary artery disease was defined as a significant stenosis on coronary angiography (≥70% stenosis) or a history of myocardial infarction. Resting ECG and blood samples for determination of creatinine, hematocrit, hemoglobin, and BNP were obtained.

Doppler echocardiography was performed at rest and under dobutamine stress as reported in detail. Cardiac output was determined by multiplication of the heart rate by the stroke volume, derived in the LV outflow tract (LVOT) from the product of the LVOT velocity-time integral and cross-sectional area. Cine loops of apical 4- and 2-chamber, parasternal long-axis, and short-axis views were obtained and the LVEF and wall motion score index were measured off-line. The LVEF was determined by the Simpson method. The wall motion score index was derived by addition of the wall motion score of each of the 16 myocardial segments (0, normal; 1, hypokinetic; 2, akinetic; 3, dyskinetic) and division by the number of visualized segments.

The therapeutic decision of valve replacement or medical treatment was left to the discretion of the treating physician. The treating physicians were blinded to the BNP measurements. A follow-up assessment for mortality was scheduled at 1 and 2 years after valve replacement or after the baseline evaluation when patients remained on medical treatment.

Patients were independently divided into groups with TS AS and PS AS based on the results of DSE. A projected EOA at normal flow rate (250 mL/s) ≤1.0 cm² was used to defined TS AS. We previously demonstrated that the projected EOA is superior to the other conventional indices (ie, EOA, gradient, and resistance) to assess stenosis severity in low-flow AS patients because it corrects for the important interindividual variability in flow rate increase that may occur during DSE.

Additionally, in patients who underwent aortic valve replacement, the severity of the stenosis was assessed by visual inspection of the valve at the time of operation as previously reported. In brief, the location and degree of commissural fusion was described and the stiffness of each valve leaflet assessed in situ to discriminate TS AS from PS AS.

#### Measurement of BNP Plasma Levels

Venous blood samples were drawn at entry visit from an antecubital vein into chilled ethylene-diamine-tetra-acetic acid Vacutainer test tubes after 30 minutes of rest with patients in a supine position. Samples were placed immediately on ice and plasma separation was performed at −4°C. Plasma samples were frozen at −70°C until assay. BNP was determined by a commercially available fluorescence immunoassay (Triage BNP Test, Biosite Diagnostics, Inc, San Diego, Calif). Relation of BNP levels to DSE findings and clinical outcome were studied.

#### Statistical Analysis

Continuous variables are expressed as mean±SD unless otherwise noted. EOA indicates indexed EOA; MG, mean gradient.

### Table 1. Patient Characteristics at Baseline

<table>
<thead>
<tr>
<th></th>
<th>Low Flow (n=69)</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>70±10</td>
</tr>
<tr>
<td>Female/male</td>
<td>13/56</td>
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<tr>
<td>EOA, cm²</td>
<td>0.94±0.23</td>
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<tr>
<td>iEOA, cm²/m²</td>
<td>0.51±0.12</td>
</tr>
<tr>
<td>PG rest, mm Hg</td>
<td>36±14</td>
</tr>
<tr>
<td>MG rest, mm Hg</td>
<td>21±8</td>
</tr>
<tr>
<td>LVEF %</td>
<td>29±10</td>
</tr>
<tr>
<td>Cardiac output, L/min</td>
<td>4.14±1.22</td>
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<tr>
<td>Mean transvalvular flow rate, mL/s</td>
<td>195±52</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>118±20</td>
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<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>72±11</td>
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<tr>
<td>NYHA functional class, n (%)</td>
<td>7 (10)</td>
</tr>
<tr>
<td>I</td>
<td>22 (32)</td>
</tr>
<tr>
<td>II</td>
<td>34 (49)</td>
</tr>
<tr>
<td>III</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>53 (77)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>43 (62)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>24 (35)</td>
</tr>
<tr>
<td>BNP, pg/mL, median (Q1 to Q3)</td>
<td>523 (239 to 971)</td>
</tr>
</tbody>
</table>

Values expressed as mean±SD unless otherwise noted. iEOA indicates indexed EOA; MG, mean gradient.

### Notes

- **TABLE 1.** Patient Characteristics at Baseline

- **Methods**

- **Patients and Study Protocol**

- **Measurement of BNP Plasma Levels**

- **Statistical Analysis**

- **Notes**
The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

**Results**

**BNP Plasma Levels**

BNP was markedly higher in this series of patients with low-flow, low-gradient AS (median [Q1 to Q3]: 523 pg/mL [239 to 971]) compared with the data reported in the literature for AS patients with preserved LV function (converted from pmol/L: 97 pg/mL [48 to 152];


9143 pg/mL [70 to 278];


and 97 pg/mL [58 to 228]). Nonetheless, the BNP values varied widely in our series. No significant differences were observed between women (n = 13; 459 pg/mL [200 to 995]) and men (n = 56; 534 pg/mL [310 to 963]).

**Relationship Between BNP and Echocardiographic Parameters**

BNP was inversely related to EF at rest (r = −0.59, P < 0.0001) and at peak stress (r = −0.51, P < 0.0001), stroke volume (r = −0.33, P = 0.006), and mean transvalvular flow rate (r = −0.31, P = 0.01); it was directly related to the wall motion score index (r = 0.36, P = 0.004). BNP was inversely related to EOA at rest (r = −0.50, P < 0.0001) and at peak stress (r = −0.46, P = 0.0002), and directly related to valvular resistance (r = 0.42, P = 0.0006). However, BNP was not significantly related to age, weight, body surface area, or presence of coronary artery disease (Table 2).

**BNP in Truly Severe and Pseudosevere Aortic Stenosis**

BNP was significantly higher in the 29 patients with TS AS compared with the 40 patients with PS AS as classified by DSE (743 pg/mL [471 to 1356] versus 394 pg/mL [191 to 906], P = 0.012). However, the overlap between groups was considerable (Figure 1A). There were no significant differences in EF (28 ± 8 versus 29 ± 9%), presence of coronary artery disease, or New York Heart Association functional class between groups. TS AS patients had, however, higher mean gradients (TS AS 26 ± 7 versus PS AS 16 ± 6 mm Hg, P < 0.0001). Of 29 patients referred for aortic valve replacement, 20 patients were classified as TS AS and 9 patients as PS AS in DSE.

Among patients who underwent aortic valve replacement, BNP levels were also significantly higher in 14 patients with TS AS compared with 11 patients with PS AS as defined by the surgeon at the time of valve replacement (829 pg/mL [523 to 1340] versus 374 pg/mL [239 to 949], P = 0.04); the intraoperative assessment of stenosis severity was not performed in 4 patients. Again, the overlap of values was considerable (Figure 1B).

**BNP and Outcome**

Patients were followed for 411 ± 343 days (1 to 1147 days). Aortic valve replacement was performed in 29 patients 67 ± 83 days (2 to 340 days) after study entry at the discretion of their treating physician. Surgically treated patients had higher BNP levels than those managed conservatively (691 pg/mL [436 to 1130] versus 422 pg/mL [188 to 948], P < 0.0001). Of 29 patients referred for aortic valve replacement, 20 patients were classified as TS AS and 9 patients as PS AS as defined by DSE (691 pg/mL [436 to 1130] versus 422 pg/mL [188 to 948], P < 0.0001). Of 29 patients referred for aortic valve replacement, 20 patients were classified as TS AS and 9 patients as PS AS as defined by DSE (691 pg/mL 436 to 1130) versus 422 pg/mL [188 to 948], P < 0.0001). Of 29 patients referred for aortic valve replacement, 20 patients were classified as TS AS and 9 patients as PS AS as defined by DSE (691 pg/mL 436 to 1130) versus 422 pg/mL [188 to 948], P < 0.0001).

**TABLE 2. BNP and Relation to Echocardiographic and Clinical Variables**

<table>
<thead>
<tr>
<th>Variable</th>
<th>BNP r</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>Effective orifice area</td>
<td></td>
<td></td>
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<tr>
<td>Rest</td>
<td>−0.50</td>
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<tr>
<td>Peak stress</td>
<td>−0.46</td>
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<td>Mean gradient</td>
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<td></td>
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<tr>
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<td>0.15</td>
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<tr>
<td>Peak stress</td>
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<tr>
<td>Valvular resistance</td>
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<td></td>
</tr>
<tr>
<td>Rest</td>
<td>0.42</td>
<td>0.0006</td>
</tr>
<tr>
<td>Peak stress</td>
<td>0.36</td>
<td>0.003</td>
</tr>
<tr>
<td>Left ventricular ejection fraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>−0.59</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Peak stress</td>
<td>−0.51</td>
<td>&lt;0.0001</td>
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<tr>
<td>Stroke volume</td>
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<td></td>
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<tr>
<td>Rest</td>
<td>−0.33</td>
<td>0.006</td>
</tr>
<tr>
<td>Peak stress</td>
<td>−0.22</td>
<td>0.07</td>
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<tr>
<td>Mean transvalvular flow rate</td>
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<td></td>
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<tr>
<td>Rest</td>
<td>−0.31</td>
<td>0.01</td>
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<tr>
<td>Peak stress</td>
<td>−0.29</td>
<td>0.02</td>
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<tr>
<td>Wall motion score index</td>
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<tr>
<td>Rest</td>
<td>0.36</td>
<td>0.004</td>
</tr>
<tr>
<td>Peak stress</td>
<td>0.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age</td>
<td>0.12</td>
<td>0.32</td>
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<tr>
<td>Weight</td>
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<td>0.17</td>
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<tr>
<td>Body surface area</td>
<td>−0.07</td>
<td>0.55</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>0.07</td>
<td>0.54</td>
</tr>
<tr>
<td>No. of vessels</td>
<td>0.06</td>
<td>0.61</td>
</tr>
</tbody>
</table>

r = Spearman correlation coefficient.

P = 0.046). The surgical patients were also younger (66 ± 11 years versus 73 ± 9 years, P = 0.006) and had lower EOA (0.83 ± 0.18 cm² versus 0.98 ± 0.24 cm², P = 0.002), whereas their LVEF was similar (28 ± 9% versus 29 ± 9%, P = 0.57).

During follow up, 20 patients died after 154 ± 142 days (5 to 416 days). Nine of these patients were in the surgical group (death 64 ± 93 days after surgery, 1 to 269 days). All deaths were of cardiac cause. Postoperative follow-up of patients who survived valve replacement was 541 ± 295 days (11 to 998 days).

BNP was significantly higher in the 20 patients who died during follow-up compared with 49 survivors (850 pg/mL [740 to 1124] versus 422 pg/mL [210 to 928], P = 0.004). Patients who died were also older (74 ± 9 versus 68 ± 10 years, P = 0.03), had smaller body surface area (1.77 m² versus 1.91 m², P = 0.02) and smaller indexed EOA (0.45 ± 0.12 cm²/m² versus 0.53 ± 0.12 cm²/m², P = 0.02), whereas LVEF was similar in nonsurvivors and survivors (26 ± 8% versus 29 ± 9%, P = 0.15).

Median BNP levels tended to be higher in the subgroup of 9 patients who died after aortic valve replacement compared with the 20 surgical survivors (Figure 2); however, this difference did not reach statistical significance (794 pg/mL [698 to 1639] versus 422 pg/mL [366 to 1186]). However,
among patients who died after valve replacement, significantly more had a baseline BNP ≥550 pg/mL compared with those who survived (8 of 9 [89%] versus 8 of 20 [40%], \( P = 0.02 \)). No significant difference in age (68 ± 10 years versus 65 ± 11 years, \( P = 0.37 \)) or LVEF (25 ± 9% versus 28 ± 8%, \( P = 0.38 \)) was observed between groups. Patients who died postoperatively, however, had lower preoperative aortic valve EOAs (0.74 ± 0.14 cm² versus 0.89 ± 0.18 cm², \( P = 0.04 \)). In 16 patients in whom postoperative BNP was available, a marked decrease in BNP was observed (baseline BNP 717 pg/mL [414 to 1407], postoperative BNP 278 pg/mL [106 to 488], \( P = 0.003 \)) at a mean follow-up of 8.9 ± 7.3 months postoperatively.

In the entire patient population, 33 (48%) patients had a baseline BNP ≥550 pg/mL. There was no significant difference in age (71 ± 10 years versus 69 ± 11 years, \( P = 0.25 \)), but differences in New York Heart Association functional class (2.8 ± 0.6 versus 2.3 ± 0.9, \( P = 0.01 \)), EOA (0.81 ± 0.21 cm² versus 0.98 ± 0.20 cm², \( P = 0.001 \)) and LVEF (24 ± 9% versus 33 ± 6%, \( P < 0.0001 \)) were observed between the groups with BNP ≥550 pg/mL compared with BNP <550 pg/mL. Table 3 depicts the relationship between BNP <550 pg/mL or ≥550 pg/mL and survival in patients with TS AS and PS AS treated medically or surgically. The subgroups were too small

<table>
<thead>
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<th>Group</th>
<th>BNP &lt;550 pg/mL</th>
<th>BNP ≥550 pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>TS AS</td>
<td>Patients, n</td>
<td>Deaths, n</td>
</tr>
<tr>
<td>Medical treatment</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Valve replacement</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>PS AS</td>
<td>Patients, n</td>
<td>Deaths, n</td>
</tr>
<tr>
<td>Medical treatment</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Valve replacement</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

TS AS indicates truly severe aortic stenosis; PS AS, pseudo-severe aortic stenosis.
for statistical analyses; however, a consistent pattern of higher mortality was observed in patients with BNP ≥550 pg/mL.

Survival at 1 year was very poor in patients with BNP ≥550 pg/mL (47±9%) but surprisingly good in those with BNP <550 pg/mL (97±3%, P<0.0001) (Figure 3A). The same was true when the subgroups with surgical and medical treatment were considered. Cumulative 1-year survival was 39±13% in medically treated patients with BNP ≥550 pg/mL but 100% in those with BNP <550 pg/mL (Figure 3B). In the surgically treated group, 30-day mortality was 19% in patients with BNP ≥550 pg/mL versus 8% in those with BNP <550 pg/mL, and 1-year survival was 53±13% versus 92±7% (Figure 3C).

In 36 patients with contractile reserve defined by increase of stroke volume ≥20% at peak DSE, 1-year survival was strikingly lower in patients with BNP ≥550 pg/mL (48±12%) compared with those with BNP <550 pg/mL (93±6%) (Figure 3D). The same pattern was observed in the subset (n=32) of patients with no or poor contractile reserve (50±14% versus 100%).

Only age ≥70 years (P=0.015), New York Heart Association class ≥2 (P=0.006), resting EOA ≤0.8 cm² (P=0.005), poor contractile reserve defined by a peak transvalvular flow rate <250 mL/s on DSE (P=0.0017), and BNP ≥550 pg/mL (P<0.001) were significant predictors of outcome for the total cohort. A trend was observed for diabetes (P=0.05). Gender, coronary artery disease, LVEF, aortic valve replacement, and projected indexed EOA were not significantly related to outcome. Of note, BNP level was the most powerful predictor of outcome. However, the number of patients was too small to perform multivariate analysis and thus confirm the independent contribution of this variable to the prediction of outcome.

**Discussion**

**Low-Flow, Low-Gradient Aortic Stenosis: A Diagnostic and Therapeutic Challenge**

It is well known that AS can be successfully treated by valve replacement even at a late stage of disease when LV dysfunction has developed. Connolly et al. demonstrated in a large group of patients with AS and EF <35% that surgery can be performed with acceptable operative mortality and that most patients will have an improvement in symptoms and LV function. However, most patients in this series had relatively high gradients (mean gradient >40 mm Hg) despite a mark-
edly reduced EF. There is however a small subset of patients who present with small valve areas, which indicates severe AS but low gradients caused by a low flow rate, and who have a high operative mortality of 8% to 33% and a higher chance of remaining in congestive heart failure after surgery.\textsuperscript{3-5,13} It has been hypothesized that patients primarily improve when LV dysfunction is the result of afterload mismatch associated with AS, but they may not benefit when the LV dysfunction is caused by other myocardial disease.\textsuperscript{25}

In the latter patients the valve stenosis may not even be severe. Rather, the valve may be only mild to moderately diseased and may not open fully because of the low driving forces. Thus the separation of TS AS from PS AS is considered critical for the selection of patients for surgery. The response of valve area and gradient to a dobutamine-induced flow increase can help distinguish between TS AS and PS AS;\textsuperscript{10,11} however, this differentiation remains difficult. More important, it is still not clear whether distinction between these entities is the appropriate basis for the decision to operate on a patient. The French multicenter study\textsuperscript{3,12} on low-flow, low-gradient AS demonstrated that the assessment of contractile reserve during DSE provides important information for patient risk stratification. From their first report,\textsuperscript{12} it appeared that only patients with contractile reserve should undergo surgery, as these patients were likely to have a good outcome after valve replacement, whereas survival was poor in patients without contractile reserve regardless of whether or not they had surgery. In the second larger series, however, the same authors\textsuperscript{9} reported that outcome, although poor overall, was still significantly better with surgery, even in the group without contractile reserve. More recently, the same group published a third study that showed that although the absence of LV contractile reserve is associated with an increased operative mortality, most of the survivors manifest an improvement in symptoms and LVEF.\textsuperscript{9,13} The authors therefore concluded that the absence of contractile reserve is useful for operative risk stratification, but that it should not preclude consideration for aortic valve replacement. However, from these data, it remained unclear how to identify those patients in the subgroup with no contractile reserve who benefit from surgery. Thus, current research should focus on better criteria to decide between valve replacement and medical treatment or eventual heart transplantation in this difficult patient subset.

Natriuretic Peptides in Aortic Stenosis

Natriuretic peptides are independent predictors of outcome in a variety of heart disease such as congestive heart failure, acute myocardial infarction, and coronary artery disease, as well as pulmonary embolism and primary pulmonary hypertension.\textsuperscript{26-32} In AS, natriuretic peptides have recently been shown to correlate with stenosis severity, severity of symptoms, and LV dysfunction.\textsuperscript{15-22} In asymptomatic patients with severe AS, BNP and N-terminal-proBNP predict the onset of symptoms and may therefore be helpful to select patients for early elective surgery.\textsuperscript{20} Furthermore, neurohormones determined prior to valve replacement predict postoperative outcome with regard to survival, postoperative symptomatic status, and postoperative LV function.\textsuperscript{20} Increased BNP has also recently been reported to be a risk factor for poor postoperative outcome in other adult cardiac surgery.\textsuperscript{33} These results raise the question whether BNP can also (1) risk-stratify patients with low-flow AS, (2) help distinguish TS AS from PS AS, and (3) possibly help identify patients who benefit from valve replacement and those who would benefit more from medical treatment. However, no data have been available for this difficult patient subset.

BNP in Low-Flow, Low-Gradient Aortic Stenosis

The present study is, to our knowledge, the first to examine BNP in low-flow, low-gradient AS. Similar to previous studies in other patient populations, BNP was inversely related to measures of LV function such as EF, stroke volume, and transvalvular flow.\textsuperscript{26,27} Similar to other studies in patients with AS, BNP also increased with stenosis severity and demonstrated an inverse relation to valve area and direct relation to valve resistance.\textsuperscript{17-19} Furthermore, BNP was significantly higher in TS AS than PS AS. This may be caused by the more extensive LV afterload in patients with more severe AS. Increased wall stress and myocardial stretch have been shown to release BNP, which has been referred to as the only “true” ventricular hormone, in various cardiac entities\textsuperscript{26-28} and also in previous studies of AS.\textsuperscript{14,16} Patients with TS AS had indeed higher gradients, whereas EF was similar in both groups. Because BNP increases with the severity of LV damage of any cause, it is not surprising that the overlap of BNP levels between PS AS and TS AS was too extensive to allow their differentiation in individual patients. In patients in whom postoperative BNP was available, a marked decline from baseline levels was observed after valve replacement, which supports the hypothesis of BNP release in response to wall stress and afterload.

The most important finding of the present study is the relationship between BNP and survival in low-flow, low-gradient AS. BNP $\geq$550 pg/mL was found to be the strongest predictor of survival when New York Heart Association functional class, LVEF, contractile reserve, type of treatment (surgical or medical), and other clinical variables such as coronary artery disease or diabetes were considered. The high prognostic value of BNP was found in the patient subset who underwent surgery as well as in the subset treated medically. Patients who underwent surgery and had BNP levels $<$550 pg/mL had an excellent 1-year survival (92±7%). However, surgical patients with BNP $\geq$550 pg/mL were found to have a 1-year survival of only 53±13%. Although this was still higher than in patients with similar BNP levels treated medically (39±13%), such poor outcome may indicate that heart transplantation should perhaps be considered as an alternative treatment in some patients of this high-risk group, if eligible for this therapy. In addition, it remains to be determined whether the utilization of less invasive techniques such as percutaneous or transapical valve replacement\textsuperscript{34,35} would help reduce short-term mortality in the low-flow AS patients with BNP $\geq$550 pg/mL. However, more data are required before BNP can be used for therapeutic recommendations. The fact that patients with a low BNP have a good outcome in both the surgically and medically treated groups should not lead to the conclusion that valve replacement is of
no benefit in this subset of patients. Importantly, the baseline characteristics of these 2 groups are different. In particular, the majority of patients who underwent surgery had TS AS, whereas most patients treated medically had PS AS. Hence, our results can only support the conclusion that low BNP predicts a favorable outcome in patients who are likely to have TS AS and undergo surgery and in patients who are likely to have PS AS and are treated medically.

Interestingly, patients both with and without contractile reserve (defined as previously proposed by an increase of stroke volume ≥20% at peak DSE) had a good outcome as long as BNP was <550 pg/mL. On the other hand, outcome was poor in both groups when BNP was ≥550 pg/mL. Thus, it appears that BNP adds critical information beyond the contractile reserve assessment. BNP may help to identify those patients in the difficult subset of patients without contractile reserve who are likely to benefit from valve replacement.

**Study Limitations**

The population size of the present study is relatively small. However, larger studies in these very ill patients are difficult to achieve because low-flow AS is encountered in only about 5% of AS patients and follow-up is often limited by their dismal prognosis.

The therapeutic decision in the present study was left to the discretion of the treating physicians. However, a randomized treatment would not have been appropriate for ethical reasons. Importantly, treating physicians were blinded to the BNP measurements.

**Conclusion**

BNP is markedly elevated in low-flow, low-gradient AS and is related to variables of LV function and AS severity. BNP is significantly higher in TS AS compared with PS AS and predicts survival in the entire patient group, as well as postoperative outcome in those patients who undergo valve replacement. Survival is very poor in both surgically and medically treated patients when BNP is ≥550 pg/mL. Furthermore, in patients without contractile reserve, outcome is significantly reduced in patients with BNP ≥550 pg/mL. Therefore, BNP may provide important information for therapeutic decision-making in low-flow, low-gradient AS beyond commonly used clinical and DSE variables.

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**Disclosures**

None.

**References**


**CLINICAL PERSPECTIVE**

Patients with low-flow, low-gradient aortic stenosis represent the most challenging subset of patients with aortic stenosis to manage. Dobutamine stress echocardiography has been shown to be useful to distinguish truly severe from pseudosevere aortic stenosis and to assess myocardial contractile reserve. Although the absence of contractile reserve is associated with a high operative mortality, most of the survivors manifest an improvement of symptoms and left-ventricular systolic function. However, it remains unclear how to identify patients with poor contractile reserve who are likely to benefit from aortic valve replacement. In the present study, a plasma level of B-type natriuretic peptide ≥550 pg/mL was associated with markedly reduced survival in both medically and surgically treated patients. Moreover, patients without contractile reserve defined by an increase of stroke volume <20% on dobutamine stress echocardiography had a good outcome as long as B-type natriuretic peptide was <550 pg/mL. On the other hand, outcome was poor in both patients with contractile reserve and those without contractile reserve when B-type natriuretic peptide was ≥550 pg/mL. Therefore, B-type natriuretic peptide may provide useful information that will aid in therapeutic decision-making in low-flow, low-gradient aortic stenosis beyond commonly used clinical and dobutamine stress echocardiography variables.
B-Type Natriuretic Peptide in Low-Flow, Low-Gradient Aortic Stenosis: Relationship to Hemodynamics and Clinical Outcome: Results From the Multicenter Truly or Pseudo-Severe Aortic Stenosis (TOPAS) Study

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