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Risk Score for Predicting Outcome in Patients With Asymptomatic Aortic Stenosis

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Valvular Heart Disease

Risk Score for Predicting Outcome in Patients With Asymptomatic Aortic Stenosis

Jean-Luc Monin, MD, PhD; Patrizio Lancellotti, MD, PhD; Mehran Monchi, MD; Pascal Lim, MD; Emmanuel Weiss, MD; Luc Piérard, MD, PhD; Pascal Guéret, MD

Background—The management of patients with asymptomatic severe aortic stenosis remains controversial. We sought to develop a continuous risk score for predicting the midterm development of symptoms or adverse events in this setting.

Methods and Results—We prospectively followed 107 patients with asymptomatic aortic stenosis (aged 72 years [63 to 77]; 35 women; aortic-jet velocity, 4.1 m/s [3.5 to 4.4]) at a single center in France. Predefined end points for assessing outcome were the occurrence within 24 months of death or aortic valve replacement necessitated by symptoms or by a positive exercise test. Variables independently associated with outcome were used to build a score that was validated in an independent cohort of 107 patients from Belgium. Independent predictors of outcome were female sex, peak aortic-jet velocity, and B-type natriuretic peptide at baseline. Accordingly, the score could be calculated as follows: Score=[peak velocity (m/s)×2]+(natural logarithm of B-type natriuretic peptide×1.5)+1.5 (if female sex). Event-free survival after 20 months was 80% for patients within the first score quartile compared with only 7% for the fourth quartile. Areas under the receiver operating characteristic curve for the score were 0.90 and 0.89 in the development and validation cohorts, respectively.

Conclusions—If further validation is achieved, this score may be useful to predict outcome in individual patients with asymptomatic aortic stenosis to select those who might benefit from early surgery. (***Circulation***. 2009;120:69-75.)

Key Words: echocardiography ■ natriuretic peptides ■ risk score ■ stenosis ■ valves

According to current guidelines, severe symptomatic aortic stenosis (AS) is a straightforward indication for valve replacement.[1,2] In contrast, the decision to operate on asymptomatic patients remains a source of debate.[1,2] The risk of sudden death without preceding symptoms remains a matter of concern,[3] as well as the risk of irreversible myocardial damage due to left ventricular (LV) hypertrophy.[4] Furthermore, the potential for rapid disease progression and excess mortality in patients with even moderate AS has been pointed out recently.[5] Prospective studies have demonstrated the poor midterm outcome of asymptomatic patients with high peak aortic-jet velocity at baseline[6] or moderate to severe valve calcification.[7] The prognostic value of B-type natriuretic peptide (BNP) serum level, reflecting LV end-systolic wall stress, has also been evaluated.[8–12] However, no single value is an absolute criterion to define hemodynamic severity or to predict the development of symptoms because functional capacity in AS is the result of a complex interplay between the aortic valve, the LV, and the systemic vasculature.[13] Thus, to select the patients who are likely to benefit from early surgery, a continuous score integrating valve and ventricular-related parameters might be more appropriate. Therefore, we prospectively followed 107 asymptomatic patients with moderate to severe AS at a single center in France. Independent predictors of outcome were integrated to build a continuous risk score, designed to predict the midterm development of symptoms or other adverse events. This score was then validated in an independent set of 107 patients from Belgium.

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Methods

Patients

The development cohort consisted of 107 consecutive patients referred to the Echocardiography Laboratory at Henri Mondor University Hospital (Créteil, France) and prospectively enrolled on the basis of the following criteria: (1) moderate to severe AS, defined[1] by a peak aortic-jet velocity ≥3.0 m/s and/or aortic valve area ≤1.5 cm²; (2) absence of symptoms; (3) normal LV function defined by an ejection fraction ≥50% without segmental wall motion abnormality by echocardiography; (4) normal sinus rhythm; (5) no more than mild associated cardiac valve lesion; and (6) serum creatinine <160 µmol/L. The validation cohort included 107 consecutive patients with asymptomatic AS, who were prospectively followed at Sart Tilman University Hospital (Liège, Belgium). Both

centers used the same inclusion criteria, the same protocol for echocardiographic and BNP measurements, and the same indications for valve replacement according to current guidelines.[2] This study was approved by both local institutional ethics committees, and written informed consent was obtained from all patients before enrollment.

Echocardiography

Comprehensive Doppler echocardiography, including M-mode, 2-dimensional echocardiography, color Doppler, and pulsed-wave and continuous-wave Doppler measurements, was performed in all patients at baseline and at each follow-up visit. Patients in the development cohort were evaluated mainly by a single senior echocardiographer (J.-L.M.; 90% of examinations) with the use of commercially available systems. In 17 patients, the baseline echocardiography was repeated by the same physician after 25 (18 to 37) days. Thus, intraobserver variability was as follows (mean±SD): LV outflow tract diameter, 0.1±0.5 mm; LV outflow tract time-velocity integral, 0±3 cm; peak aortic-jet velocity, 0.0±0.3 m/s; mean transaortic pressure gradient, −1±6 mm Hg; and aortic valve area, 0.01±0.09 cm². The suspected origin of AS was determined according to current criteria.[7] Peak aortic-jet velocity was derived from transaortic flow, recorded with continuous-wave Doppler with a multiwindow approach.[6] Aortic valve area was calculated by the continuity equation[14] and indexed to body surface area. The degree of aortic valve calcification was assessed from echocardiographic zoomed short-axis views and scored on a 4-grade scale according to Rosenhek et al.[7]

Exercise Testing

Symptom-limited graded bicycle exercise tests were performed at inclusion in 89 patients (83%) of the development cohort. After an initial workload of 25 W maintained for 2 minutes, the load was increased by steps of 25 W every 2 minutes. Twelve-lead ECG was monitored continuously and recorded every 2 minutes with blood pressure measurements. The exercise test was considered abnormal if any of the following events occurred during exercise: dyspnea, angina, syncope or near syncope; insufficient rise in systolic blood pressure (<20 mm Hg) or fall in blood pressure compared with baseline; <80% of the normal level of exercise tolerance according to age- and sex-adjusted levels; ≥2 mm horizontal or downsloping ST-segment depression compared with rest; ventricular tachycardia or >4 premature ventricular complexes in a row.[15]

BNP Measurements

Venous blood samples for BNP were drawn before echocardiography or any exercise test after 20 minutes of supine rest. Chilled ethylenediaminetetra-acetic acid tubes were centrifuged immediately at 4000*g* (4°C) for 15 minutes. Separated plasma samples were processed by immunofluorescence assay (Beckman-Coulter, Biosite). The interassay and intra-assay variations were 5% and 4%, respectively. The assay detection limit was 1 pg/mL.

Follow-Up

Follow-up visits were scheduled every 6 to12 months, according to guidelines.[1,2] Each visit included a clinical evaluation, BNP measurements, Doppler echocardiography, and exercise testing (if indicated and applicable). Valve replacement was indicated according to current guidelines (ie, occurrence of symptoms or abnormal exercise test [symptoms or abnormal blood pressure response during exercise]).[2] Predefined end points for assessing outcome in the development cohort were the occurrence within 24 months after enrollment of death (any cause) or aortic valve replacement necessitated by symptoms or by a positive exercise test.[2] We chose a 24-month period because it seemed to be the shortest clinically relevant interval for delaying surgery according to a "wait-for-symptom" strategy.

Statistical Analysis

Descriptive data are reported as proportions for qualitative variables and median (quartile 1 to quartile 3) for continuous variables, unless otherwise indicated. In the development cohort, baseline variables previously described as associated with outcome (age,[7] sex,[16] cause of AS and calcification score,[7] peak velocity, mean transaortic pressure gradient and valve area,[3,6] and BNP serum level[8,10,11]) were screened for association with the 24-month end point. We used χ^2 tests for categorical data. To assess the relationship between each numerical variable and the 24-month end point, we first plotted continuous variables against the 24-month end point, and we used the Lowess smoothing function with locally weighted least squares to identify proportional relationships. The results of this procedure indicated that for BNP, a natural logarithm transformation is needed for proportionality. The associations linking numerical variables to the 24-month end point were evaluated by Mann-Whitney *U* tests. *P* values <0.05 were considered statistically significant. All statistical tests were 2-tailed.

Variables significantly associated with outcome in univariable analysis were included in a multiple logistic regression model.[17–19] We used backward elimination of nonsignificant variables to define a simple score. Then the β coefficient of each of the variables independently associated with a 24-month end point was used to build the score.[20]

Finally, we evaluated the score performance to predict the 24-month composite end point in the development cohort and an independent validation cohort of 107 patients. To evaluate discrimination, the area under the receiver operating characteristic curve was determined.[21] To evaluate calibration, Hosmer-Lemeshow goodness-of-fit tests using 5 quintiles of poor outcome were performed.

Results

Characteristics and Outcomes in the Development Cohort

In the development cohort, follow-up information was available for 104 patients (97%). On the basis of patient history and echocardiographic analysis, the suspected origin of AS was calcification of a 3-leaflet (n=75), bicuspid (n=22), or unicuspid (n=1) aortic valve, rheumatic disease (n=2), radiotherapy (n=2), or undetermined (n=2). According to current guidelines, AS was severe or moderate in 75 and 29 patients, respectively. Predefined end points were reached in 62 patients within 8 months (5 to 13) including 3 deaths, 58 aortic valve replacements, and 1 patient who refused surgery despite development of symptoms and a positive exercise test. Of note, 90% of outcomes in this group (n=56) occurred before 20 months. One patient died postoperatively (operative mortality, 2%) at day 4 from right ventricular failure. In contrast, 42 patients remained free of clinical event after 32 months (26 to 45) of follow-up. Patients' characteristics according to outcome are given in Table 1.

Deaths Before Surgery

Three patients from the development cohort died before surgery. A 79-year-old man with moderate AS (peak velocity, 3.9 m/s; aortic valve area, 1.1 cm²; BNP, 245 pg/mL) died of pneumonia after 6 months. A 75-year-old woman with severe AS (peak velocity, 4.6 m/s; aortic valve area, 0.7 cm²; BNP, 56 pg/mL) died of bowel cancer at 10 months. A 71-year-old man with moderate AS (peak velocity, 3.5 m/s; aortic valve area, 1.2 cm²; BNP, 34 pg/mL) died of aortic endocarditis at 14 months.

Valve Replacement Indicated by Exercise Test Results

Valve replacement was indicated for an abnormal exercise test at baseline in 11 patients (aged 76 years [70 to 78]; peak

Table 1. Characteristics of the 104 Patients Prospectively Followed in the Development Cohort, According to the 24-Month End Point

Characteristic*	Whole Group (n=104)	Remained Asymptomatic (n=42)	End Point Within 24 Months (n=62)	P
Age, y	72 [63–77]	70 [53–77]	74 [65–78]	0.16
Female sex, n (%)	35 (34)	9 (21)	26 (42)	0.03
Serum BNP, pg/mL	58 [30–111]	30 [14–64]	83 [47–165]	0.0001
BNP at first follow-up, pg/mL	66 [32–173]	36 [16–71]	161 [64–242]	0.0001
Creatinine, μmol/L	96 [84–109]	97 [85–106]	94 [83–116]	0.97
Aortic valve anatomy				0.002
Three-leaflet valve, n (%)	75 (72)	23 (55)	52 (84)	
Bicuspid aortic valve, n (%)	22 (21)	13 (31)	9 (15)	
Calcification score 3 to 4, n (%)	72 (69)	24 (57)	48 (77)	0.01
Peak velocity, m/s	4.1 [3.5–4.4]	3.6 [3.2–4.0]	4.3 [3.9–4.6]	0.0001
Progression in peak velocity, m/s per year	0.3 [0.0–0.5]	0.2 [0.0–0.4]	0.4 [0.1–0.6]	0.27
Mean pressure gradient, mm Hg	40 [31–50]	33 [24–40]	47 [36–55]	0.0001
Valve area, cm^2	0.9 [0.8–1.1]	1.1 [1.0–1.3]	0.8 [0.7–1.0]	0.0001
Indexed area, cm^2/m^2	0.5 [0.4–0.6]	0.6 [0.5–0.7]	0.5 [0.4–0.5]	0.0001
LV end-diastolic diameter, mm	51 [47–53]	51 [48–52]	50 [47–53]	0.67
LV end-systolic diameter, mm	29 [27–32]	29 [26–32]	29 [27–33]	0.50
Interventricular septum (diastole), mm	12 [11–13]	12 [11–13]	12 [11–13]	0.48
LV posterior wall (diastole), mm	12 [11–13]	12 [10–13]	12 [11–13]	0.24
LV ejection fraction, %	67 [62–72]	68 [65–72]	66 [60–70]	0.08
Known coronary artery disease, n (%)	23 (22)	10 (24)	13 (21)	0.87
Diabetes mellitus, n (%)	13 (12)	4 (10)	9 (15)	0.42
Hypertension, n (%)	58 (56)	22 (52)	36 (58)	0.48
Hypercholesterolemia, n (%)	38 (37)	16 (38)	22 (35)	0.83

Values in square brackets are quartile 1 to quartile 3.

*Characteristics are given at baseline unless indicated otherwise.

velocity, 4.1 m/s [3.7 to 4.5]; BNP, 175 pg/mL [62 to 240]). These tests were considered positive for dyspnea (n=3), fall of systolic blood pressure (n=4), or insufficient rise in blood pressure (n=4, associated with significant ST depression in 2 cases). These 11 patients underwent surgery within 2 months (1 to 4). Seven other patients underwent surgery within 9 months (7 to 14) for an abnormal exercise test during follow-up (insufficient rise in blood pressure in 5 or dyspnea in 2).

Other Indications for Valve Replacement

Aortic valve replacement was necessitated by the development of symptoms in 37 patients within 10 months (7 to 16) (dyspnea, n=32; angina pectoris, n=3 including 1 patient with associated dyspnea; syncope, n=2). Four patients (aged 67 years [65 to 73]; 3 women; peak aortic-jet velocity, 4.3 m/s [4.0 to 4.4]; serum BNP, 38 pg/mL [36 to 48]) underwent valve replacement within 3 months (1 to 6) after enrollment, without symptom or positive exercise test. Surgery was performed at the discretion of the referring physician in 3 cases, whereas the fourth patient was a 31-year-old woman with severe AS who wanted to schedule pregnancy. Data from these 4 latter patients were censored at the time of valve replacement.

Predictors of Outcome/Building of the Risk Score

Variables associated with the 24-month end point by univariable and multivariable analysis are given in Table 2. Accord-

ing to multivariable analysis, 3 parameters were independent predictors of outcome: female sex, serum BNP, and peak aortic-jet velocity at baseline. For each individual patient, a risk score was calculated according to the following formula: Score=[peak velocity (m/s)×2]+(natural logarithm of BNP×1.5)+1.5 (if female sex). Of note, there were no threshold values for the continuous variables included in the model (Figures I and II in the online-only Data Supplement). Kaplan–Meier analysis of symptom-free survival according to the score quartiles in the development cohort is shown in Figure 1.

Characteristics and Outcomes in the Validation Cohort

The validation cohort consisted of 107 consecutive patients with the following baseline characteristics: age, 71 years (66 to 78); 42 women (39%); peak aortic-jet velocity, 4.1 m/s (3.7 to 4.6); aortic valve area, 0.8 cm^2 (0.7 to 0.9); mean pressure gradient, 42 mm Hg (34 to 49); serum BNP, 59 pg/mL (33 to 113). The suspected origin of AS was calcification of a 3-leaflet valve (n=93), bicuspid aortic valve (n=12), or rheumatic disease (n=2). Events occurred in 56 patients within 11 months (7 to 16), including 5 deaths, 41 valve replacements, and 10 patients who developed symptoms (3 refused surgery, and 7 were on the waiting list at the time of last follow-up). The median follow-up duration in the vali-

Table 2.   Predictors of Outcome in the Development Cohort by Univariable and Multivariable Analysis

Variable	Univariable Analysis		Multivariable Analysis	
	Odds Ratio (95% CI)	P	Odds Ratio (95% CI)	P
Female sex	2.65 (1.08–6.5)	0.03	5.21 (1.46–18.6)	0.01
Serum BNP*	4.0 (2.2–7.2)	0.0001	3.87 (1.84–8.1)	0.0001
Three-leaflet valve	4.3 (1.7–10.7)	0.002	2.34 (0.56–9.7)	0.24
Calcification score 3–4	3.1 (1.3–7.5)	0.01	2.11 (0.61–7.2)	0.23
Peak velocity†	5.4 (2.45–11.8)	0.0001	6.2 (2.1–17.9)	0.001
Transaortic mean pressure gradient‡	1.09 (1.05–1.13)	0.0001	1.14 (0.93–1.39)	0.22
Aortic valve area§	0.59 (0.47–0.74)	0.0001	0.86 (0.63–1.16)	0.32
Indexed valve area‖	0.42 (0.28–0.63)	0.0001	0.7 (0.4–1.2)	0.23

Variables are given at baseline unless indicated otherwise. CI indicates confidence interval.

*Odds ratios are expressed per log unit increase in marker levels.

†Odds ratios are expressed per 1 unit increase >2.

‡Odds ratios are expressed per 1 unit increase >10.

§Odds ratios are expressed per 0.1 increase >0.5.

‖Odds ratios are expressed per 0.1 increase >0.3.

dation sample was 21 months. Of note, 90% of outcomes (n=50) occurred before 20 months in this group. Five patients from the validation cohort died before surgery (Table 3), all from cardiac causes (congestive heart failure, n=2; sudden death, n=2; acute pulmonary edema, n=1). One patient died postoperatively (operative mortality, 2%). Valve replacement was necessitated by the development of symptoms in 29 patients within 11 months (7 to 14). The main symptoms were dyspnea, angina pectoris, or syncope in 18, 8, and 3 patients, respectively. In the remaining 12 patients, surgery was performed for new onset of atrial fibrillation (n=1), positive exercise test (n=6), or equivocal symptoms (n=5). In contrast, 51 patients remained free of clinical event after 21 months (18 to 27) of follow-up. The median value of the risk score in the validation cohort was 14.9 (13.5 to 16.5). Of note, the score values of all 5 patients who died before surgery were in the third and fourth score quartiles (Table 3). Kaplan–Meier analysis of symptom-free survival according to the score quartiles in the validation cohort is given in Figure 2. This analysis shows a progressive decrease of midterm event-free survival according to each score quartile, without significant difference compared with the validation cohort.
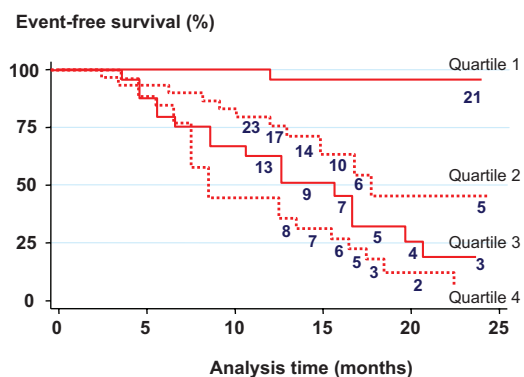
Figure 1. Kaplan–Meier analysis of symptom-free survival according to the score quartiles in the development cohort. The respective values for score quartiles 1 to 4 were 12.9, 14.6, 16.2, and 19.7. Numbers below each slope represent the patients at risk at each time point.

Prognostic Value of the Score Over its Range

By pooling the development and the validation cohorts (n=211 patients), the median score value was 14.8 (13.2 to 16.3). The adverse event rate according to continuous score values in this combined cohort is shown in Figure 3. This figure shows a low event rate (<10%) for score values <11, with a steep linear increase between 11 and 16 a slower increase in the high-risk range (>75%) for values >16.

Score Performances in the Development and Validation Cohorts

The area under the receiver operating characteristic curve for the score was 0.90 (95% confidence interval, 0.84 to 0.96) in the development cohort and 0.89 (95% confidence interval, 0.84 to 0.96) in the validation cohort, indicating a good discrimination, with a significant improvement in both cohorts compared with peak velocity or BNP levels when considered alone (Table 4).

Discussion

The decision to operate on asymptomatic patients with severe AS remains a source of debate. The rationale for a wait-for-symptom strategy is supported by the rarity of sudden death without preceding symptoms.[3,7,22] Therefore, the combined risks of surgery and prosthesis-related events probably outweigh the risk of sudden death in a truly asymptomatic patient.[1,2] However, there is a risk of death while the patient is on the waiting list for surgery[7] and a risk of progressive and eventually irreversible myocardial damage.[4] Therefore, risk stratification is clinically important.

In this study, we developed a risk score based on the 3 independent predictors of midterm outcome in a population of asymptomatic patients with mostly severe AS. According to this score, 80% of patients within the first quartile remained free from events after 20 months of follow-up. In contrast, only 7% of patients within the fourth score quartile remained free of events after 20 months.

Independent Predictors of Outcome in Asymptomatic AS

Our results confirm the high prognostic impact of peak aortic-jet velocity at baseline to predict the occurrence of

Table 3. Characteristics and Outcomes in the 5 Patients Who Died Before Surgery in the Validation Cohort

Sex	Age, y	Peak Velocity, m/s	Serum BNP, pg/mL	Score Value	Follow-Up Duration, mo	Cause of Death
Male	84	3.4	521	16.1	9	Heart failure
Male	77	4.0	123	15.2	6	Pulmonary edema
Male	78	4.3	229	16.8	8	Heart failure
Female	68	5.6	71	19.1	13	Sudden death
Female	49	4.8	116	18.3	19	Sudden death

symptoms or adverse events.[6] In contrast to the findings of Rosenhek et al,[7] neither the annual rate of progression in peak velocity nor the degree of valve calcification was independently predictive of outcome in the present study. This might be explained for 2 main reasons. First, because of the wider range of velocities at the time of inclusion in this study, the prognostic impact of baseline velocity might preclude the effect of its annual progression. Second, the most powerful predictor of outcome in our study (ie, serum BNP) was not assessed by Rosenhek et al.[7]

In contrast to previous studies,[3,5–7] we found that female sex was independently predictive of the midterm development of symptoms. This observation is in agreement with the results of Hachicha et al,[16] who found a higher prevalence of women among patients with paradoxical low-flow, low-gradient AS despite normal LV function, a condition associated with a significantly worse outcome compared with patients with normal flow.[16] In addition, Legget et al[23] found that despite similar hemodynamic severity, women with AS reported more functional impairment, with a shorter exercise duration and lower anaerobic threshold. This may be due to a relatively smaller LV cavity and increased relative wall thickness that could be associated with higher filling pressures and a lower increase in cardiac output during exercise.[23] Moreover, an interaction between sex and serum BNP values has also been suggested by some other reports.[24,25]

Previous studies have demonstrated the relationship between BNP serum levels and the hemodynamic severity of AS,[11] the presence of symptoms,[10,11] or clinical outcome.[8,11] To our knowledge, this is the first prospective study demon-

strating the incremental prognostic value of BNP level over peak aortic-jet velocity in a relatively large cohort of patients with asymptomatic AS.

Rationale for Utilizing a Risk Score
The risk score developed in the present study is based largely on the combination of 2 quantitative variables reflecting hemodynamic severity at baseline at both the aortic valve and ventricular levels. Intentionally, we sought to assess all potential predictors available at baseline to predict midterm outcome. The rationale for this is that some patients may become symptomatic before the first follow-up visit; thus, follow-up parameters would not be appropriate in this case. In contrast to every single measurement that cannot predict the development of symptoms, this score might better reflect the complex interplay between the LV and the aortic valve.[13] Furthermore, the good reproducibility and independent prognostic value of both variables have been demonstrated previously.[3,8,10,11,26] Of note, all 5 preoperative deaths from the validation cohort were due to cardiac causes, presumably related to AS (sudden death or heart failure). More importantly, the score values of these 5 patients were all in the third and fourth score quartiles (n=2 and 3, respectively). This result supports the fact that earlier surgery in these high-risk patients might have prevented some of these deaths. The rationale for utilizing this score rather than logistic models relies on its robustness for predicting clinical outcome and its simplicity. For research purposes as well as for the clinician, this score is easier to use than the sophisticated logistic models on which it was built. Further validation on large cohorts of patients will only require computing their baseline characteristics including sex, peak aortic velocity, and serum
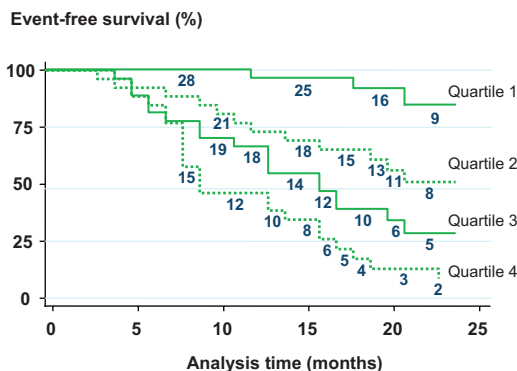
Figure 2. Kaplan–Meier analysis of symptom-free survival according to the score quartiles in the validation cohort. The quartiles values of the development cohort were taken for this analysis.
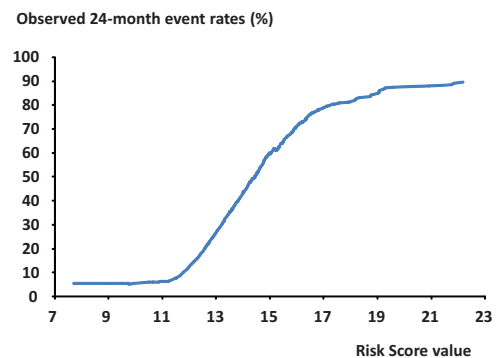
Figure 3. Observed event rate at 24 months in the combined cohort (n=211 patients) according to continuous risk score values.

Table 4. Score Performances for the Prediction of the 24-Month End Point by Logistic Regression

	Area Under the ROC Curve	Hosmer-Lemeshow Goodness-of-Fit Test
Development cohort		
BNP	0.79 (0.70–0.88)	$\chi^2=3.35, P=0.35$
Peak aortic-jet velocity	0.77 (0.68–0.87)	$\chi^2=6.75, P=0.08$
Risk score	0.90 (0.84–0.96)*	$\chi^2=1.5, P=0.68$
Validation cohort		
BNP	0.84 (0.77–0.91)	$\chi^2=6.05, P=0.11$
Peak aortic-jet velocity	0.61 (0.49–0.71)	$\chi^2=0.99, P=0.80$
Risk score	0.89 (0.84–0.96)†	$\chi^2=2.74, P=0.43$

ROC indicates receiver operating characteristic. 95% confidence intervals are shown in parentheses.

*$P=0.003$ vs BNP, $P=0.0032$ vs peak aortic-jet velocity.

†$P=0.045$ vs BNP, $P=0.0001$ vs peak aortic-jet velocity.

BNP to assess the corresponding score values against outcome. In addition, if this validation is achieved, such a score could be easily implemented as a risk calculator for bedside use to stratify risk in individual patients.

Limitations of the Study

A limitation of this study might be the relatively small number of patients included in the development cohort compared with previous prospective studies on asymptomatic AS.[6,7] In addition, the average follow-up duration in the validation cohort was 21 months, which is slightly shorter than the 24-month follow-up duration on which the score was initially developed. However, given that 90% of the outcomes occurred before 20 months in both cohorts, we think that they are comparable. Furthermore, our results demonstrate the excellent discrimination and calibration of this score to predict midterm outcome, both in the development cohort and in an independent validation cohort. Another limitation might be the inclusion of patients with moderate AS in the development cohort. Of note, most of the patients in this cohort (72%) had severe AS. Furthermore, the inclusion of patients with moderate AS is clinically relevant, given the potential for rapid disease progression and excess mortality in these patients.[5]

Conclusions

Although further validation is needed to fit with different healthcare systems or other techniques of measurement of BNP, this score may already be useful in its present form to stratify risk in patient cohorts before randomization in a prospective study. Finally, if further validation is achieved, this score may be useful to predict outcome in individual patients with asymptomatic AS to select those who might benefit from early surgery.

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Disclosures

None.

References

1. Bonow RO, Carabello BA, Kanu C, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O'Gara PT, O'Rourke RA, Otto CM, Shah PM, Shanewise JS, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Antman EM, Fuster V, Halperin JL, Hiratzka LF, Hunt SA, Nishimura R, Page RL, Riegel B. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2006;114:e84–e231.
2. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, Flachskampf F, Hall R, Iung B, Kasprzak J, Nataf P, Tornos P, Torracca L, Wenink A, Priori SG, Blanc JJ, Budaj A, Camm J, Dean V, Deckers J, Dickstein K, Lekakis J, McGregor K, Metra M, Morais J, Osterspey A, Tamargo J, Zamorano JL, Angelini A, Antunes M, Fernandez MA, Gohlke-Baerwolf C, Habib G, McMurray J, Otto C, Pierard L, Pomar JL, Prendergast B, Rosenhek R, Uva MS. Guidelines on the management of valvular heart disease: the Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. *Eur Heart J*. 2007;28:230–268.
3. Pellikka PA, Sarano ME, Nishimura RA, Malouf JF, Bailey KR, Scott CG, Barnes ME, Tajik AJ. Outcome of 622 adults with asymptomatic, hemodynamically significant aortic stenosis during prolonged follow-up. *Circulation*. 2005;111:3290–3295.
4. Lund O, Erlandsen M, Dorup I, Emmertsen K, Flo C, Jensen FT. Predictable changes in left ventricular mass and function during ten years after valve replacement for aortic stenosis. *J Heart Valve Dis*. 2004;13:357–368.
5. Rosenhek R, Klaar U, Schemper M, Scholten C, Heger M, Gabriel H, Binder T, Maurer G, Baumgartner H. Mild and moderate aortic stenosis. Natural history and risk stratification by echocardiography. *Eur Heart J*. 2004;25:199–205.
6. Otto CM, Burwash IG, Legget ME, Munt BI, Fujioka M, Healy NL, Kraft CD, Miyake-Hull CY, Schwaegler RG. Prospective study of asymptomatic valvular aortic stenosis: clinical, echocardiographic, and exercise predictors of outcome. *Circulation*. 1997;95:2262–2270.
7. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, Maurer G, Baumgartner H. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med*. 2000;343:611–617.
8. Bergler-Klein J, Klaar U, Heger M, Rosenhek R, Mundigler G, Gabriel H, Binder T, Pacher R, Maurer G, Baumgartner H. Natriuretic peptides predict symptom-free survival and postoperative outcome in severe aortic stenosis. *Circulation*. 2004;109:2302–2308.
9. Gerber IL, Legget ME, West TM, Richards AM, Stewart RA. Usefulness of serial measurement of N-terminal pro-brain natriuretic peptide plasma levels in asymptomatic patients with aortic stenosis to predict symptomatic deterioration. *Am J Cardiol*. 2005;95:898–901.
10. Gerber IL, Stewart RA, Legget ME, West TM, French RL, Sutton TM, Yandle TG, French JK, Richards AM, White HD. Increased plasma natriuretic peptide levels reflect symptom onset in aortic stenosis. *Circulation*. 2003;107:1884–1890.
11. Lim P, Monin JL, Monchi M, Garot J, Pasquet A, Hittinger L, Vanoverschelde JL, Carayon A, Gueret P. Predictors of outcome in patients with severe aortic stenosis and normal left ventricular function: role of B-type natriuretic peptide. *Eur Heart J*. 2004;25:2048–2053.
12. Weber M, Arnold R, Rau M, Elsaesser A, Brandt R, Mitrovic V, Hamm C. Relation of N-terminal pro B-type natriuretic peptide to progression of aortic valve disease. *Eur Heart J*. 2005;26:1023–1030.
13. Otto CM. Valvular aortic stenosis: disease severity and timing of intervention. *J Am Coll Cardiol*. 2006;47:2141–2151.
14. Skjaerpe T, Hegrenaes L, Hatle L. Noninvasive estimation of valve area in patients with aortic stenosis by Doppler ultrasound and two-dimensional echocardiography. *Circulation*. 1985;72:810–818.
15. Iung B, Gohlke-Bärwolf C, Tornos P, Tribouilloy C, Hall R, Butchart E, Vahanian A. Recommendations on the management of the asymptomatic patient with valvular heart disease. *Eur Heart J*. 2002;23:1253–1262.
16. Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. *Circulation*. 2007;115:2856–2864.
17. Lemeshow S, Teres D, Avrunin JS, Gage RW. Refining intensive care unit outcome prediction by using changing probabilities of mortality. *Crit Care Med*. 1988;16:470–477.
18. Lemeshow S, Teres D, Klar J, Avrunin JS, Gehlbach SH, Rapoport J. Mortality probability models (MPM II) based on an international cohort of intensive care unit patients. *JAMA*. 1993;270:2478–2486.

19. Lemeshow S, Teres D, Pastides H, Avrunin JS, Steingrub JS. A method for predicting survival and mortality of ICU patients using objectively derived weights. *Crit Care Med*. 1985;13:519–525.
20. Hosmer D, Lemeshow S. *Applied Logistic Regression*, 1st ed. New York: John Wiley & Sons; 1989.
21. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143:29–36.
22. Horstkotte D, Loogen F. The natural history of aortic valve stenosis. *Eur Heart J*. 1988;9:57–64.
23. Legget ME, Kuusisto J, Healy NL, Fujioka M, Schwaegler RG, Otto CM. Gender differences in left ventricular function at rest and with exercise in asymptomatic aortic stenosis. *Am Heart J*. 1996;131:94–100.
24. Maisel AS, Clopton P, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, Omland T, Storrow AB, Abraham WT, Wu AH, Steg G, Westheim A, Knudsen CW, Perez A, Kazanegra R, Bhalla V, Herrmann HC, Aumont MC, McCullough PA. Impact of age, race, and sex on the ability of B-type natriuretic peptide to aid in the emergency diagnosis of heart failure: results from the Breathing Not Properly (BNP) multinational study. *Am Heart J*. 2004;147:1078–1084.
25. Christ M, Laule-Kilian K, Hochholzer W, Klima T, Breidthardt T, Perruchoud AP, Mueller C. Gender-specific risk stratification with B-type natriuretic peptide levels in patients with acute dyspnea: insights from the B-type natriuretic peptide for acute shortness of breath evaluation study. *J Am Coll Cardiol*. 2006;48:1808–1812.
26. Otto C. Aortic stenosis: echocardiographic evaluation of disease severity, disease progression, and the role of echocardiography in clinical decision making. In: Otto C, ed. *The Practice of Clinical Echocardiography*. Philadelphia: WB Saunders; 1997:405–432.

CLINICAL PERSPECTIVE

The decision to operate on asymptomatic patients with severe aortic stenosis remains a source of debate. The risk of sudden death without preceding symptoms remains a matter of concern as well as the risk of irreversible myocardial damage due to severe left ventricular hypertrophy. In the present study, we developed a risk score based on the 3 independent predictors of midterm outcome (ie, sex, peak aortic-jet velocity, and serum B-type natriuretic peptide) in a population of 104 consecutive patients with mostly severe aortic stenosis who were asymptomatic at baseline and prospectively followed. This score was then validated on an independent cohort of 107 consecutive patients. According to this score, 80% of patients within the first quartile remained free from events after 20 months of follow-up. In contrast, only 7% of patients within the fourth score quartile remained free of events after 20 months. The rationale for utilizing this score rather than logistic models relies on its robustness for predicting clinical outcome and its simplicity. Although further validation is needed, this score may already be useful in its present form to stratify risk in patient cohorts before randomization in a prospective study. Finally, if further validation is achieved, this score may be useful to predict outcome in individual patients with asymptomatic aortic stenosis to select those who might benefit from early surgery.
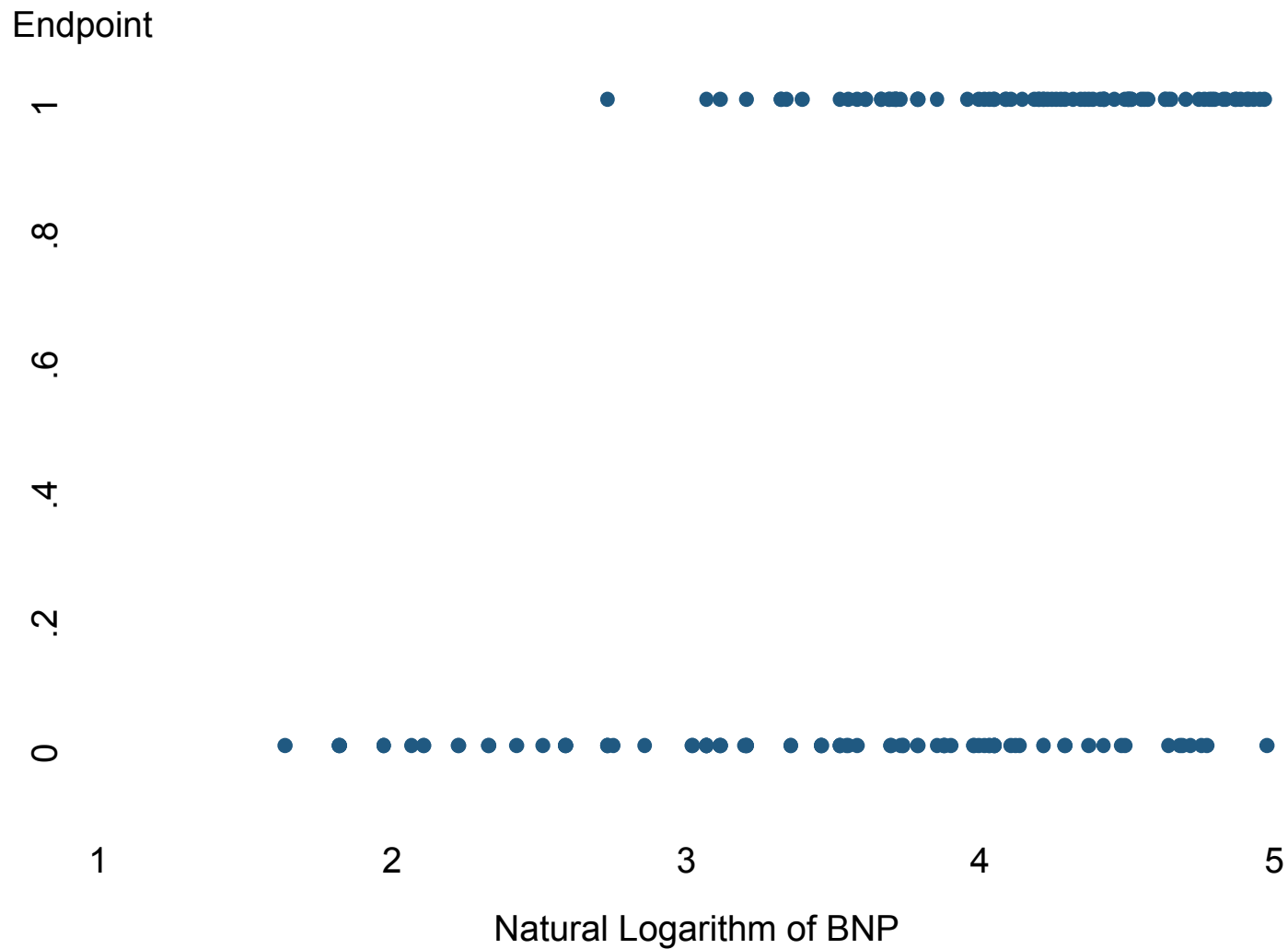
Supplemental Figure 1: Lowess smoother graph of the relationship between natural logarithm of BNP and 24-month endpoint (bandwidth = .8)
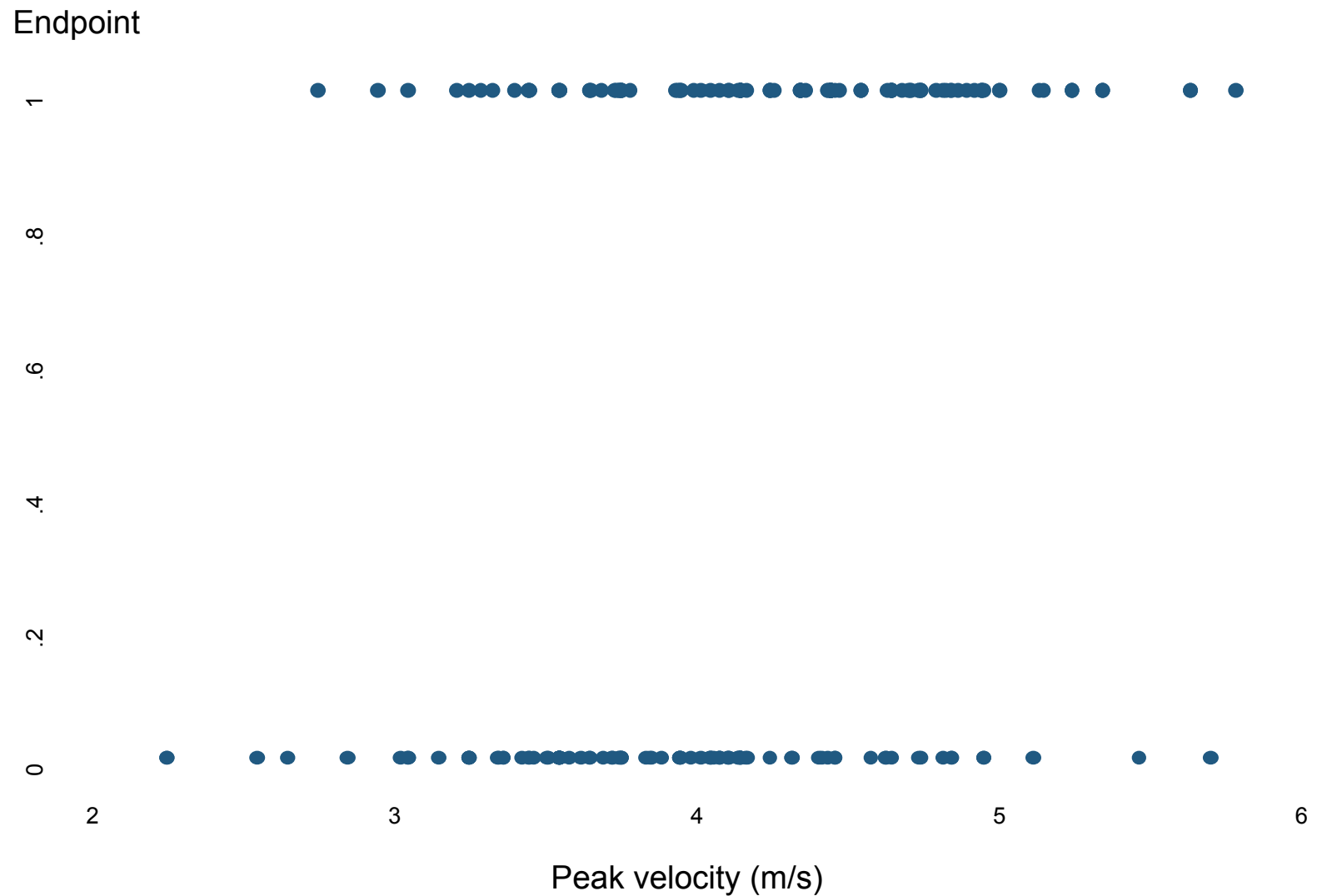
Supplemental Figure 2: Lowess smoother graph of the relationship between Peak aortic-jet velocity (m/s) and 24-month endpoint (bandwidth = .8)