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A Risk Prediction Model in Asymptomatic Patients with Severe Aortic Stenosis:

CURRENT-AS risk score

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Abstract

Objective: Early aortic valve replacement (AVR) might be beneficial in selected high-risk asymptomatic patients with severe aortic stenosis (AS), considering their poor prognosis when managed conservatively. This study aimed to develop and validate a clinical scoring system to predict AS-related events within 1-year after diagnosis in asymptomatic severe AS patients.

Methods: We analysed 1274 asymptomatic severe AS patients derived from a retrospective multicentre registry enrolling consecutive patients with severe AS in Japan (CURRENT AS registry), who were managed conservatively and completed 1-year follow-up without AVR. From a randomly assigned derivation set (N=849), we developed CURRENT AS risk score for the AS-related event (a composite of AS-related death and heart failure hospitalization) within 1-year using a multivariable logistic regression model.

Results: The risk score comprised independent risk predictors including left ventricular ejection fraction <60%, hemoglobin ≤11.0g/dl, chronic lung disease (2 points), diabetes mellitus, hemodialysis, and any concomitant valve disease (1 point). The predictive accuracy of the model was good with the area under the curve of 0.79 and 0.77 in the derivation and validation sets (N=425). In the validation set, the 1-year incidence of AS-related events was much higher in patients with score ≥2 than in patients with score ≤1 (Score 0: 2.2%, Score 1: 1.9%, Score 2: 13.4%, Score 3: 14.3%, and Score ≥4: 22.7%, *P*<0.001).

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Conclusions: The CURRENT-AS risk score integrating clinical and echocardiographic

factors well predicted the risk of AS-related events at 1-year in asymptomatic patients with

severe AS, and was validated internally.

Keywords: Severe aortic stenosis, asymptomatic, risk prediction model

(Contemporary Outcomes After Surgery and Medical Treatment in Patients With Severe

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Key questions

What is already known about this subject?

In asymptomatic patients with severe aortic stenosis (AS), many prognostic factors have been reported including clinical characteristics, echocardiographic parameters, and elevated plasma levels of natriuretic peptides. The risk-prediction models in asymptomatic AS patients are very limited and derived only from small patient populations that included moderate AS. There is no previous report on the risk-prediction model specific for asymptomatic patients with severe AS.

What does this study add?

(1) We developed the CURRENT AS risk score integrating the independent predictors of AS-related events at 1-year after diagnosis in asymptomatic patients with severe AS, that include diabetes mellitus, hemodialysis, any concomitant valve disease, LVEF <60%, hemoglobin ≤11 g/dl, and chronic lung disease

(2) The CURRENT AS risk score accurately predicted the risk of AS-related events at 1-year in asymptomatic patients with severe AS, and was validated internally

How might this impact on clinical practice?

Given their high 1-year AS-related event rates, asymptomatic patients with score ≥2 might be benefitted by early AVR, even when the current guidelines do not recommend it. The risk

score would be useful in selecting high-risk asymptomatic patients with severe AS for early

AVR.

Introduction

Current guidelines generally recommend a strategy of watchful waiting until indications for aortic valve replacement (AVR) emerge in asymptomatic patients with severe aortic stenosis (AS),(1, 2) because the potential benefits of AVR in asymptomatic patients with severe AS have not been thought to outweigh the operative mortality of AVR.(3, 4) However, in asymptomatic patients with severe AS, the risk of aortic valve (AV)-related death and heart failure (HF) hospitalization remains high when managed conservatively(5). Also, the rate of sudden death was substantial.(6-10) Considering their poor prognosis, early AVR might be beneficial in selected high-risk asymptomatic patients with severe AS.

In asymptomatic patients with severe AS, many prognostic factors have been reported including clinical characteristics (older age, anemia(11), presence of atherosclerotic risk factors), echocardiographic parameters (valve calcification, peak aortic jet velocity,(8, 10, 12, 13) rate of hemodynamic progression,(8) valve area, left ventricular ejection fraction,(14) increase in mean aortic pressure gradient >20mmHg with exercise,(14) excessive left ventricular hypertrophy,(15) abnormal longitudinal left ventricular function,(16) and pulmonary hypertension(17), and elevated plasma levels of natriuretic peptides.(16, 18) The practicing clinicians have to integrate these prognostic factors to make decision for early AVR or watchful waiting in asymptomatic patients with severe AS.(19, 20) Thus, risk prediction models would provide valuable information for planning an optimal

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treatment strategy. However, the risk-prediction models in asymptomatic AS patients are very

limited and derived only from small patient populations that included moderate AS.(21, 22)

There is no previous report on the risk-prediction model specific for asymptomatic patients

with severe AS. Therefore, we sought to develop a 1-year risk prediction model in

asymptomatic patients with severe AS that included comprehensive clinical and

echocardiographic parameters from a large Japanese multicenter observational database of

consecutive patients with severe AS.

Methods

Study population

CURRENT AS (Contemporary outcomes after sURgery and medical tREatmeNT in

patients with severe Aortic Stenosis) registry is a retrospective multicenter registry that

enrolled 3815 consecutive patients with severe AS from 27 centers in Japan between January

2003 and December 2011 (Appendix). The design, patient enrollment, and main result of the

registry were previously reported in detail.(5) Briefly, we searched the hospital database for

transthoracic echocardiography and enrolled consecutive patients who had met the criteria for

severe AS (peak aortic jet velocity [Vmax] >4.0 m/s, mean aortic pressure gradient (PG) >40

mm Hg, or aortic valve area [AVA] <1.0 cm^2)(1) for the first time during the study period. We

excluded patients with a history of percutaneous balloon valvuloplasty or surgical aortic

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valve repair/replacement/plasty. Among the 3815 patients enrolled in the registry, there were

1517 patients who had no AS-related symptoms and were managed conservatively at the time

of diagnosis of severe AS (Figure 1). In the present study, we sought to develop a clinical

prediction rule for the 1-year prognosis of asymptomatic patients with severe AS under

watchful waiting. The current study population consisted of 1274 asymptomatic patients who

were managed conservatively, after excluding 118 patients who died from causes other than

AS-related death within 1-year, 69 patients who received AVR before occurrence of the

primary outcome measure within 1-year, and 56 patients who were lost to follow-up within 1-

year (Figure 1). Follow-up was commenced on the day of the index echocardiography. The

specific follow-up duration of 1 year was selected because the patient risk should be re-

assessed at 1-year at the latest during watchful waiting after initial risk assessment.

The protocol was approved by the institutional review board of each participating

center. Given the retrospective nature of the study, written informed consent was waived, and

all of the patients agreed to participate in the study when contacted for follow-up. The patient

record/information was anonymized prior to analysis.

Data collection and definitions

Collection of baseline clinical information was conducted via hospital chart or

database review.(5) Symptoms related to AS were classified into angina, syncope, chronic

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exertional dyspnea, or acute HF requiring hospitalization. Follow-up data were mainly

collected via review of hospital charts; otherwise, data were collected via contact with

patients, relatives, and/or referring physicians via mail with questions regarding vital status,

symptoms, and subsequent hospitalizations.(23)

The CURRENT AS clinical events committee reviewed the documentation

concerning every death and event that occurred after enrollment. Every death was placed into

one of the 2 categories in the CURRENT AS registry: (1) cardiovascular deaths, which

consist of HF, aortic valve procedure death, myocardial infarction, sudden death, infective

endocarditis, stroke, renal failure, aortic/peripheral vascular disease, other cardiac cause, and

unknown death; and (2) non-cardiovascular deaths, which include malignancy, infection,

respiratory failure, liver failure, renal failure, bleeding, trauma, and others. (5, 24) The causes

of death were classified according to the Valve Academic Research Consortium (VARC)

definitions.(25) Sudden death was defined as unexplained death in a previously stable patient.

The decision for the initial treatment strategy, either initial AVR or conservative management,

was based on the discussion between the attending physicians and the patients/family

members.

The primary outcome measure for the present analysis was AS-related events

defined as a composite of AS-related death and HF hospitalization during the 1-year follow-

up period. AS-related death included sudden death, death caused by HF potentially related to

the aortic valve, and death due to aortic valve endocarditis.(5) Death due to aortic valve endocarditis was defined by identification of aortic valve endocarditis and subsequent death despite of the treatment. HF were defined according to the modified Framingham criteria.

All patients underwent a comprehensive 2-dimensional and doppler echocardiographic evaluation in each participating center according to the guidelines.(26) Echocardiographic data were site-reported and we had no echocardiographic core laboratory. Biplane Simpson's method of disks or the Teichholz method was used for calculating left ventricular ejection fraction (LVEF). Peak and mean aortic PG were obtained with the use of the simplified Bernoulli equation, and AVA was calculated using the standard continuity equation, and indexed to body surface area. Left ventricular mass was calculated with the formula recommended by the American Society of Echocardiography (ASE).(27) A high left ventricular mass index (LVMI) was defined as LVMI >115 g/m^2 for men and >95 g/m^2 for women, in line with the ASE recommendations, and our previous report.(15, 27)

Statistical analysis

We developed a clinical prediction rule (CURRENT AS risk score) to predict the individual patient's risk for AS-related events within 1-year after diagnosis in asymptomatic patients with severe AS. The patients were randomly divided in a 2-to-1 fashion into a derivation set (N=849) and a validation set (N=425). The categorical variables were

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presented as numbers and percentages, and were compared using a chi-square test or Fisher's

exact test between the derivation and validation sets. The continuous variables were

expressed as mean ± SD or median with interquartile range (IQR). Based on their

distributions, the continuous variables were compared using the Student's t-test or the

Wilcoxon rank sum test between the two sets. Incidence of AS-related event was estimated by

the number of patients with event within 1 year divided by the number of patients at risk.

A logistic regression model was used to identify the independent predictors of the

primary outcome events during 1-year after the index echocardiography. Continuous

variables except for age were dichotomized by the clinically relevant cut-off values. Brain

natriuretic peptide (BNP) level was not adopted as a candidate variable, because BNP values

were missing in a large proportion of patients. Missing values were considered null, because

the developed clinical prediction rules should allow risk prediction based on the available

information for any patient with any missing or uncertain variables in the real clinical

practice.(28) First, clinical and echocardiographic characteristics were compared between

patients with and without experiencing the primary outcome events. Candidate variables for

the multivariable logistic regression model included those variables that differed in the

univariate comparisons at a significance level of <0.10, as indicated in Table 1 (age, body

mass index <22, diabetes mellitus, coronary artery disease, aortic/peripheral vascular disease,

hemodialysis, hemoglobin ≤11.0, chronic lung disease, Vmax ≥4.5m/s, LVEF <60%, high

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LVMI, and any concomitant valve disease). Then, we conducted the backward model

selection procedure for potential candidates, using the 0.05 significance level, to eliminate the

variables with higher P values. We finally constructed the multivariable logistic regression

model using those variables with P<0.05.(29) The β coefficient for each variable was divided

by the smallest β coefficient and rounded to the nearest integer, which was used as the weight

of the point for each variable. The risk score for an individual patient was determined by

summing the points for each variable. We assessed the discriminatory performances of the

models by the receiver operating characteristic curve analysis in the derivation and validation

sets. We calculated the area under the receiver operating characteristic curve (AUC) of each

model in the derivation and validation sets and compared the AUC values between the 2 sets.

All the statistical analyses were conducted by physicians (E.M., and T. Kato) and a

statistician (T.M.) using JMP Pro 14 or SAS 9.4 (both SAS Institute Inc., Cary, North

Carolina). All the reported P values were 2-tailed, and P values <0.05 were considered

statistically significant.

Results

Baseline characteristics

The 1274 study patients were randomly assigned to the derivation set (849 patients)

and to the validation set (425 patients) (Figure 1). There was no significant difference in the

patient characteristics and echocardiographic parameters between the derivation and

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validation sets (Supplementary table 1).

Within 1-year after the index echocardiography, 59 patients (7.0%) developed AS-related events (HF hospitalization: 26 patients and AS-related death: 33 patients) in the derivation set. Patients who had AS-related events during follow-up were older, and more often had lower BMI, diabetes mellitus, coronary artery disease, peripheral arterial disease, renal insufficiency, anemia, moderate or severe chronic lung disease, Vmax of more than 4.5 m/s, smaller AVA, lower LVEF, higher LVMI, and any concomitant valve disease than patients without events (Table 1).

Clinical risk prediction model

The univariate correlates of the AS-related events in the derivation set included BMI<22, diabetes mellitus, coronary artery disease, peripheral artery disease, hemoglobin ≤11.0g/dl, hemodialysis, chronic lung disease, Vmax >4.5 m/s, LVEF <60%, LVMI >95 or 115 g/m^2, and any concomitant valve disease (Table 1). In the multivariable logistic regression model after backward selections, 6 variables (diabetes mellitus, hemoglobin ≤11.0g/dl, hemodialysis, chronic lung disease, LVEF <60%, and any concomitant valve disease) were identified as independent predictors of AS-related events (Table 2, and Supplementary Table 2).

The risk prediction rule assigned 2 points for LVEF <60%, hemoglobin ≤11 g/dl and

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chronic lung disease, and 1 point for diabetes mellitus, hemodialysis, and any concomitant

valve disease (Figure 2A). The risk score ranged from 0 to 9, with peaks at 0 point in the

derivation and validation sets (Figure 2B). The distribution of the risk score was comparable

in both the derivation and validation sets (Figure 2B).

Clinical outcomes at 1-year in the derivation and validation sets

For comparing clinical outcomes at 1-year, patients were classified according to the

risk scores of 0, 1, 2, 3, and ≥4 points; 0 point (derivation set: N=258, 30.4%, and validation

set: N=136, 32.0%), 1 point (derivation set: N=223, 26.3%, and validation set: N=108,

24.5%), 2 points (derivation set: N=150, 17.7%, and validation set: N=67, 15.8%), 3 points

(derivation set: N=120, 14.1%, and validation set: N=70, 16.5%), and ≥4 points (derivation

set: N=98, 11.5%, and validation set: N=44, 10.4%). In the derivation set, the 1-year

incidence of AS-related events was higher in patients with score ≥3 than in patients with

score ≤2 (Score 0: 1.2%, Score 1: 3.1%, Score 2: 4.7%, Score 3: 15.8%, and Score ≥4:

23.5%, P<0.001) (Figure 3A). In the validation set, the AS-related events occurred in 34

patients (8.0%) (HF hospitalization: 18 patients and AS-related death: 16 patients). Seven

patients were sudden death, and 10 patients were death caused by HF. In the validation set,

the 1-year incidence of AS-related events was much higher in patients with score ≥2 than in

patients with score ≤1 (Score 0: 2.2%, Score 1: 1.9%, Score 2: 13.4%, Score 3: 14.3%, and

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Score ≥4: 22.7%, *P*<0.001) (Figures 3). The AUC for the risk score was 0.79 (95%

confidence interval [CI]: 0.73-0.84) in the derivation set and 0.76 (95%CI: 0.67-0.83) in the

validation set (P=0.52) (Figure 3B).

Discussion

The main findings of this study were as follows; (1) We developed the CURRENT

AS risk score integrating the independent predictors of AS-related events at 1-year after

diagnosis in asymptomatic patients with severe AS, that include diabetes mellitus,

hemodialysis, any concomitant valve disease, LVEF <60%, hemoglobin ≤11 g/dl, and chronic

lung disease; (2) The CURRENT AS risk score accurately predicted the risk of AS-related

events at 1-year in asymptomatic patients with severe AS, and was validated internally.

In asymptomatic patients with severe AS, current guidelines recommend early AVR

based on the echocardiographic findings such as high Vmax and low LVEF.(1, 2) However,

most of the independent predictors of AS-related events at 1-year in the present study were

clinical factors except for low LVEF by echocardiography. Previous reports have suggested

that comorbidities such as anemia, hemodialysis, and malignancy are associated with higher

AS-related event risk in patients with severe AS in parallel with the increasing number of

patients with advanced age and atherosclerotic backgrounds.(11, 30, 31) Regarding the

echocardiographic factors, the decline in cardiac function was an important component for

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our scores. A substantial proportion of AS patients was reported to develop events after the decline of LVEF.(32) In contrast, the severity of AS did not emerge as the independent predictor for the AS-related events in the present study. One of the reasons for this may be that we only included patients with severe AS. Once the severity of AS exceeds a certain threshold, decompensation to pressure overload leads to a decline in left ventricular function, which might be one of the most important prognostic factors in AS patients. Further, it would be important to note that the clinical factors such as anemia, hemodialysis, and concomitant valve disease might cause hemodynamic instability.

Definitive conclusions on the role of early AVR in asymptomatic patients with severe AS should be drawn based on the on-going randomized trials (EARLY TAVR, NCT03042104; AVATAR, NCT02436655; ESTIMATE, NCT02627391).(33) However, it would be reasonable to recommend early AVR in selected high-risk asymptomatic patients with severe AS. The CURRENT AS risk score accurately stratified the risk of AS-related events at 1-year in asymptomatic patients with severe AS. The accuracy of the risk prediction model might be reasonable to be used in actual clinical practice, and the factors incorporated in the risk score were those easily obtained in daily practice. Thus, the CURRENT-AS risk score may be useful in selecting those high-risk patients suitable for early AVR. More specifically, patients with risk score≥2 would be good candidates for early AVR, considering their very high AS-related event rates at 1-year, decreasing operative mortality of AVR, and

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less invasive nature of transcatheter aortic valve implantation.

It should be acknowledged that the CURRENT AS registry consisted of Japanese patients exclusively. However, diabetes, chronic obstructive pulmonary disease, and LVEF <60% were independent determinants of all-cause mortality in 861 patients with asymptomatic severe AS in the U.S.(34) Patients with severe renal dysfunction or preoperative dialysis were associated with significantly poorer outcomes in the U.S.(35) and Australia(36). Furthermore, several recent studies have focused on the relationship between anemia and severe AS in the U.S. and Europe.(37-40) These findings were consistent with those reported in the present study; however, caution must be exercised when extrapolating the present study results derived from Japanese patients to patients outside of Japan. There was no other large dataset on the long-term outcomes of asymptomatic patients with severe AS under conservative management(5); therefore, the above-mentioned ongoing RCTs on patients with asymptomatic severe AS might address the possible external validity of the present risk score in non-Asian populations.

There are some limitations to the present study. The main limitation of the present study was its retrospective design. It is important to note that the decision for the conservative or initial AVR strategy was based on a discussion between the attending physician and heart team members with the patient and their family members. This may introduce a selection bias that is difficult to detect in a retrospective fashion and may affect the reproducibility of the

risk model in different populations. Second, there were substantial missing values for the

clinical factors such as body mass index, serum creatinine, and hemoglobin (Table 1),

because blood tests were not necessarily performed at the same timing as the

echocardiography in daily practice for outpatients. Although BNP values were associated

with long-term outcomes(18), missing values were very large (63%, N=537/849); therefore,

we were unable to include the BNP into the risk score model. Third, the lack of a core

laboratory for echocardiograms limits the reproducibility of the study and may affect external

validation. Fourth, the limited number of patients and the relatively small number of events

were a limitation to estimate the risk score. Further research is necessary to determine the

generalizability and feasibility of applying this tool in clinical settings.

Conclusions

The CURRENT-AS risk score integrating clinical and echocardiographic factors accurately

predicted the risk of AS-related events at 1-year in asymptomatic patients with severe AS,

and was validated internally.

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Acknowledgement

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Figure Legends

Figure 1. Study patient flow

CURRENT AS=Contemporary Outcomes After Surgery and Medical Treatment in Patients

With Severe Aortic Stenosis, and AVR=aortic valve replacement.

Figure 2. Components and distribution of the CURRENT AS risk score.

A) Components of the CURRENT AS risk score

B) Distribution of the CURRENT AS risk score in the derivation and validation sets

LVEF=left ventricular ejection fraction.

Figure 3. Incidences of the AS-related events within 1-year and AUC in the derivation and

validation sets according to the CURRENT AS risk score.

A) AS-related events indicated the primary outcome measure defined as a composite of AS-

related death or HF hospitalization. Incidence of AS-related event was estimated by the

number of patients with event within 1 year divided by the number of study patients.

HF=heart failure.

B) AUC for the CURRENT AS risk score in the derivation and validation sets.

Derivation set (left panel) and Validation set (right panel)

AUC=area under the receiver operating characteristic curve.

Table 1. Baseline clinical and echocardiographic characteristics of patients with versus without AS-related event within 1 year in the derivation set

Variable	Event (N=59)	No event (N=790)	P value
Clinical characteristics			
Age, years[*]	79.8 ± 8.9	77.4 ± 9.3	0.05
Age ≥75 years	43 (73)	531 (67)	0.37
Men	29 (49)	312 (39)	0.14
BMI	20.6 ± 3.6	22.1 ± 3.9	0.01
BMI <22[*]	47 (76)	456 (52)	<0.001
Hypertension	44 (75)	564 (71)	0.60
Dyslipidemia‡	17 (29)	288 (36)	0.24
Current smoking	2 (3)	36 (5)	0.68
Diabetes mellitus[*]	21 (36)	179 (23)	0.02
On insulin therapy	6 (10)	34 (4)	0.04
Coronary artery disease[*]	26 (44)	209 (26)	0.004
Prior infectious endocarditis	0	1 (0.1)	1
Atrial fibrillation or flutter	15 (25)	150 (19)	0.23
Prior symptomatic stroke	10 (17)	106 (13)	0.45
Aortic/peripheral vascular disease[*]	11 (19)	59 (7)	0.003
Serum creatinine, mg/dl	1.2 (0.75-5.5)	0.8 (0.7-1.1)	<0.001
Hemodialysis[*]	18 (31)	62 (8)	<0.001
Hemoglobin, g/dl	10.5 (9.3-12.0)	12.0 (10.8-13.2)	<0.001
Hemoglobin ≤11.0g/dl[*]	31 (67)	169 (28)	<0.001
Liver cirrhosis (Child–Pugh B or C)	0	7 (1)	1
Malignancy currently under treatment	4 (7)	28 (4)	0.21
Chest wall irradiation	1 (2)	7 (1)	0.44
Immunosuppressive therapy	3 (5)	23 (3)	0.35
Chronic lung disease (moderate or severe)[*]	5 (8)	18 (2)	0.005
Etiology of aortic stenosis, No. (%)			
Degenerative	56 (95)	713 (90)	
Congenital	1 (2)	46 (6)	0.75
Rheumatic	2 (3)	30 (4)	
Infective endocarditis	0	1 (0.1)	
Echocardiographic variables			
Vmax, m/s	3.7 ± 0.9	3.8 ± 0.7	0.91

Vmax ≥4.5m/s[*]	13 (22)	110 (14)	0.09
Vmax ≥4m/s	24 (41)	309 (39)	0.81
Peak aortic PG, mmHg	59 ± 27	58 ± 22	0.83
Mean aortic PG, mmHg	34 ± 17	32 ± 14	0.41
AVA (equation of continuity), cm^2	0.75 ± 0.18	0.80 ± 0.16	0.03
LV end-diastolic diameter, mm	47 ± 8	45 ± 6	0.048
LV end-systolic diameter, mm	32 ± 10	28 ± 6	<0.001
LVEF, %	60 ± 14	66 ± 10	<0.001
LVEF <60%[*]	26 (44)	142 (18)	<0.001
LVMI, g/ m^2	130 ± 34	115 ± 31	0.001
High LVMI[*]	39 (78)	413 (60)	0.01
Any concomitant valve disease (moderate or severe)[*]	28 (48)	243 (31)	0.008

AS-related event indicated the primary outcome measure defined as a composite of AS-related death or HF hospitalization.

[*] Candidate variables for the multivariable logistic regression model with p-values < 0.10.

‡ Dyslipidemia was defined as total cholesterol levels ≥240 mg/dl, high-density lipoprotein cholesterol levels <40 g/dl or the use of statin

Missing values included BMI in 102 patients (12%), serum creatinine in 191 patients (22%), hemoglobin in 202 patients (24%), and LVEF in 3 patients (0.4%).

AS=aortic stenosis, AVA=aortic valve area, BMI=body mass index, HF=heart failure, IQR=interquartile range, LV=left ventricular, LVEF=left ventricular ejection fraction, LVMI=left ventricular mass index, PG=pressure gradient, SD=standard deviation, and Vmax=peak aortic jet velocity.

Table 2. Univariate and Multivariable Analysis for the Independent Risk Factors for the Primary Outcome Measure in the Derivation Set

Predictors of events	Univariate	Multivariable				Points
	Odds ratio (95% CI)	β estimate	SE	Odds ratio (95% CI)	P value	Points
Diabetes mellitus	1.88 (1.06-3.27)	0.80	0.40	2.24 (1.11-4.49)	0.02	1
Hemoglobin ≤11 g/dl	5.28 (2.83-10.3)	1.48	0.35	4.39 (2.20-8.76)	<0.001	2
Hemodialysis	5.15 (2.75-9.39)	1.15	0.40	3.16 (1.45-6.90)	0.004	1
Chronic lung disease	3.97 (1.42-11.11)	1.76	0.59	5.79 (1.84-18.27)	0.003	2
LVEF <60%	3.59 (2.06-6.16)	1.37	0.35	3.94 (2.00-7.78)	<0.001	2
Any concomitant valve disease (moderate or severe)	2.03 (1.19-3.47)	0.79	0.35	2.20 (1.11-4.35)	0.02	1

CI=confidence interval, HF=heart failure, and SE=standard error.

Other abbreviations are same as in table 1.
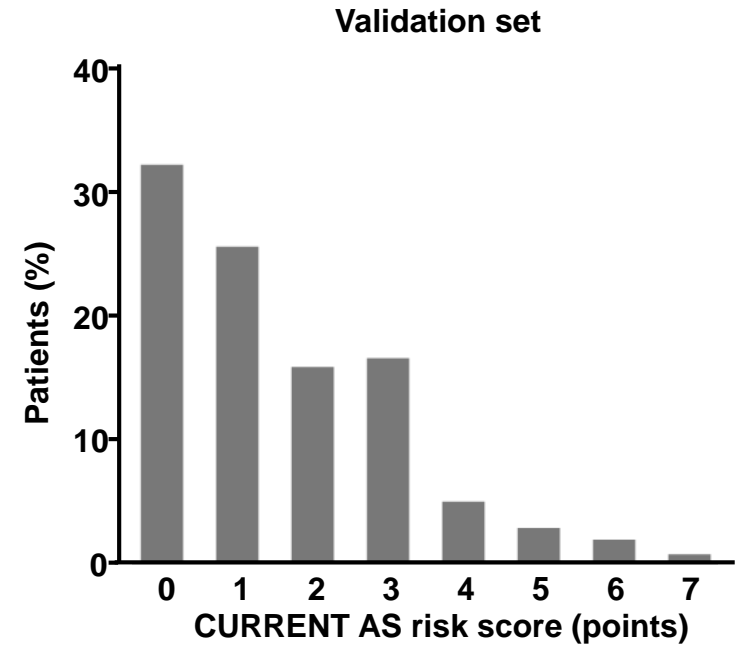
Figure 1

Figure 1. Study flow chart
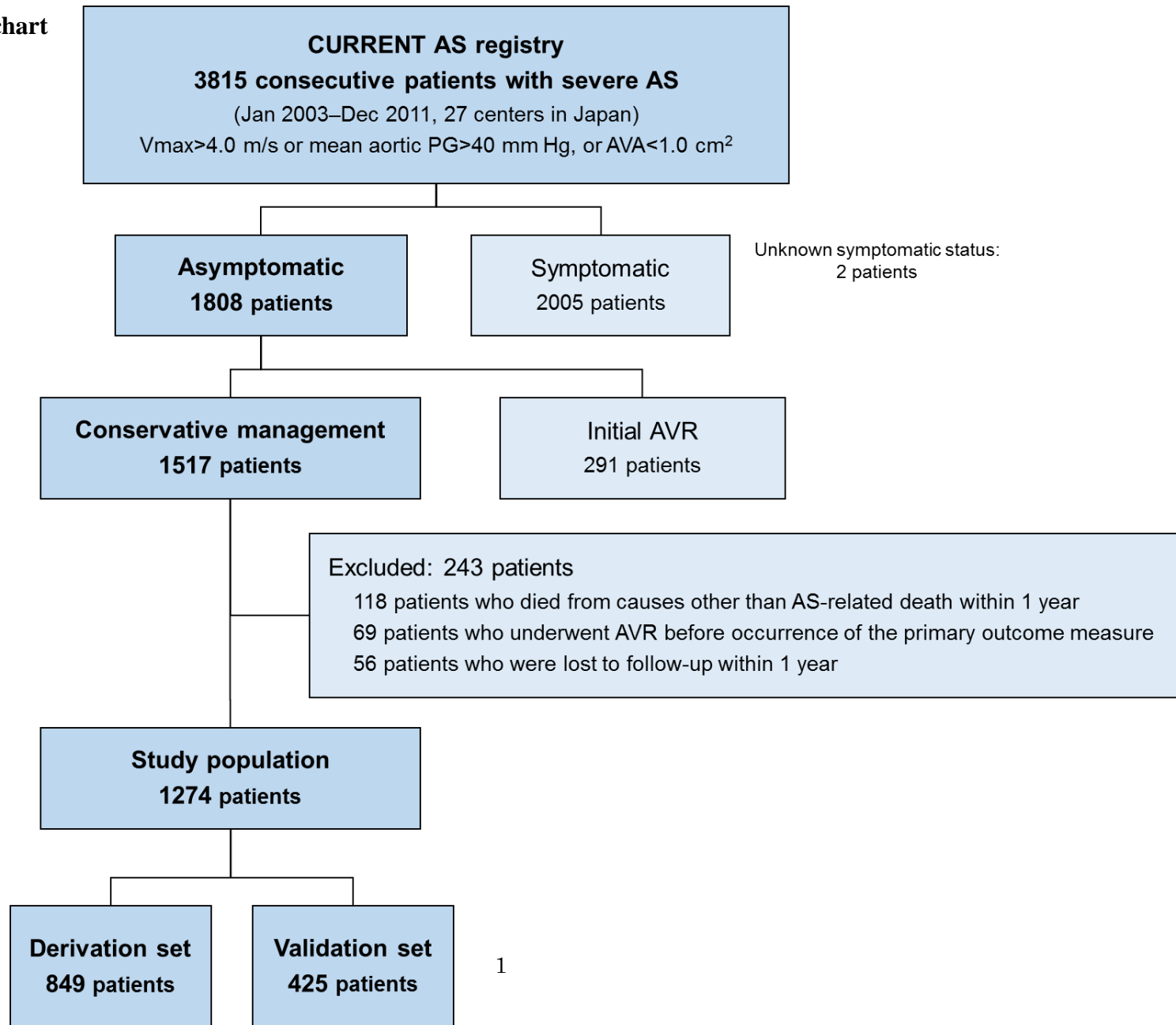
Figure 2. Components and distribution of the CURRENT AS risk score.

A) Components of the CURRENT AS risk score

Components	Points
Diabetes mellitus	1
Hemodialysis	1
Any combined valvular disease	1
LVEF <60%	2
Hemoglobin ≤11 g/dL	2
Chronic lung disease	2
Total score range: 0-9	

1

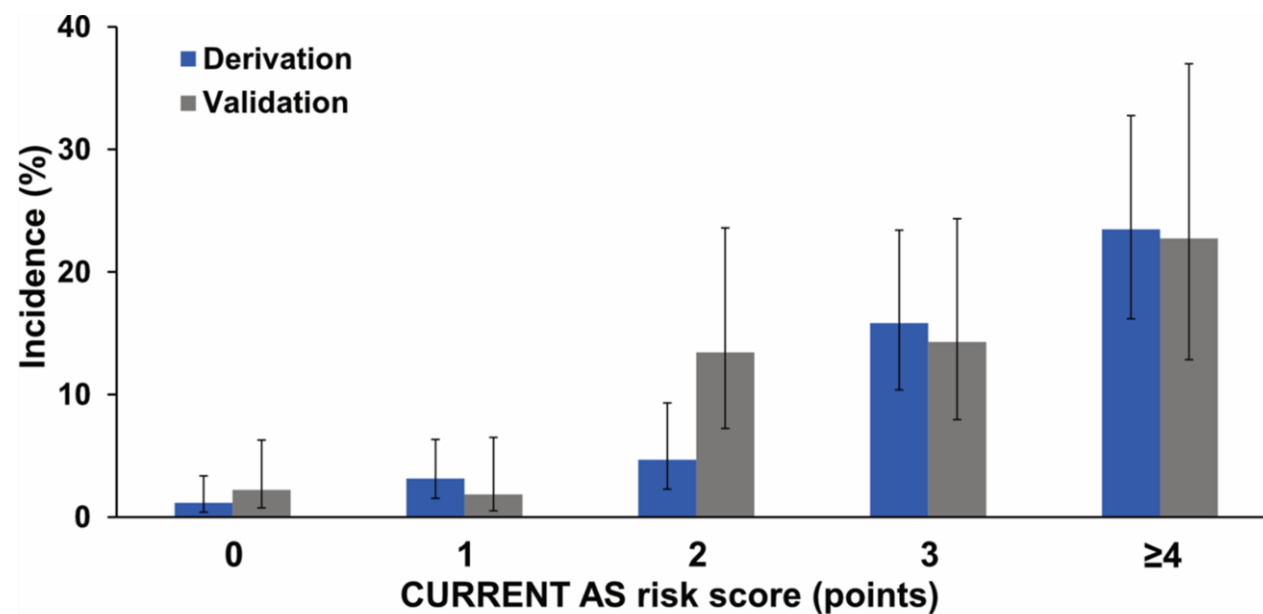**B) Distribution of the CURRENT AS risk score in the derivation and validation sets**

Derivation set
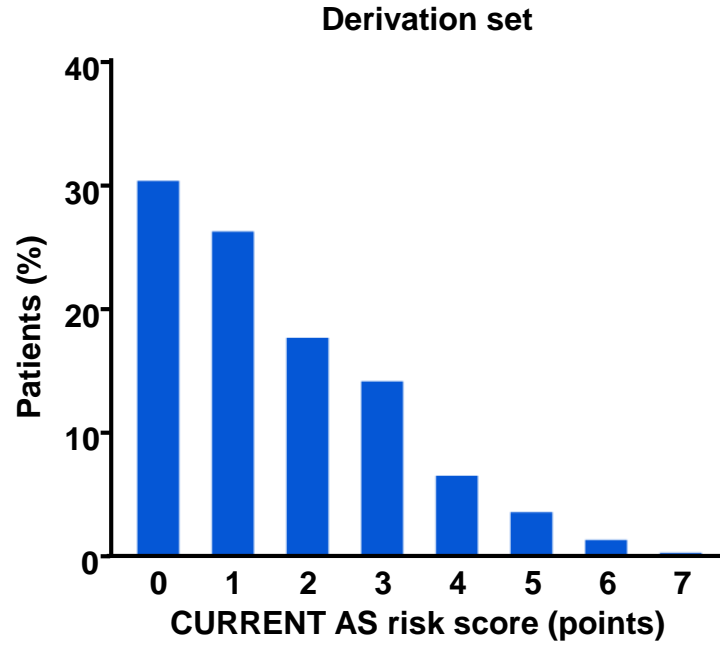
Validation set

N of patients: 849 258 223 150 120 55 30 11 2

N of patients: 425 136 108 67 70 21 12 8 3

2

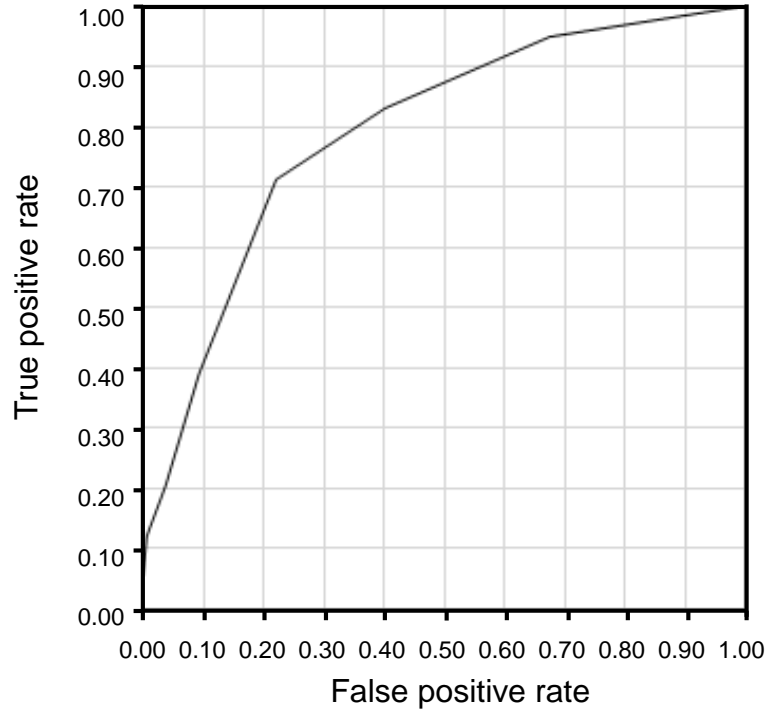Figure 3

Figure 3.

(A)

	Score (points)	0	1	2	3	4
Derivation set	Incidence	1.2%	3.1%	4.7%	15.8%	23.5%
	95%CI	0.40-3.4%	1.5-6.3%	2.3-9.3%	10.4-23.4%	16.2-32.8%
Validation set	Incidence	2.2%	1.9%	13.4%	14.3%	22.7%
	95%CI	0.75-6.3%	0.51-6.5%	7.2-23.6%	7.9-24.3%	12.8-37.0%

(B) Derivation set

Validation set