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ORIGINAL PAPER

How can progression be predicted in patients with mild to moderate aortic valve stenosis?

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Aims

The pressure increase per time unit (dP/dt) in aortic stenosis (AS) jet velocity is assumed to have inter-individual variability in the progressive AS stage. We sought to examine the association of aortic valve (AoV) Doppler-derived dP/dt in patients with mild to moderate AS with risk of progression to severe disease.

Methods and results

A total of 481 patients diagnosed with mild or moderate AS [peak aortic jet velocity (Vmax) between 2 and 4 m/s] according to echocardiographic criteria were included. AoV Doppler-derived dP/dt was determined by measuring the time needed for the pressure to increase at a velocity of the AoV jet from 1 m/s to 2 m/s. During a median follow-up period of 2.7 years, 12 of 404 (3%) patients progressed from mild to severe AS and 31 of 77 (40%) patients progressed from moderate to severe AS. AoV Doppler-derived dP/dt had a good ability to predict risk of progression to severe AS (area under the curve = 0.868) and the cut-off value was 600 mmHg/s. In multivariable logistic regression, initial AoV calcium score (adjusted odds ratio [aOR], 1.79; 95% confidence interval [CI], 1.18–2.73; $P = 0.006$) and AoV Doppler-derived dP/dt (aOR, 1.52/100 mmHg/s higher dP/dt; 95% CI, 1.10–2.05; $P = 0.012$) were associated with progression to severe AS.

Conclusion

AoV Doppler-derived dP/dt above 600 mmHg/s was associated with risk of AS progression to the severe stage in patients with mild to moderate AS. This may be useful in individualized surveillance strategies for AS progression.

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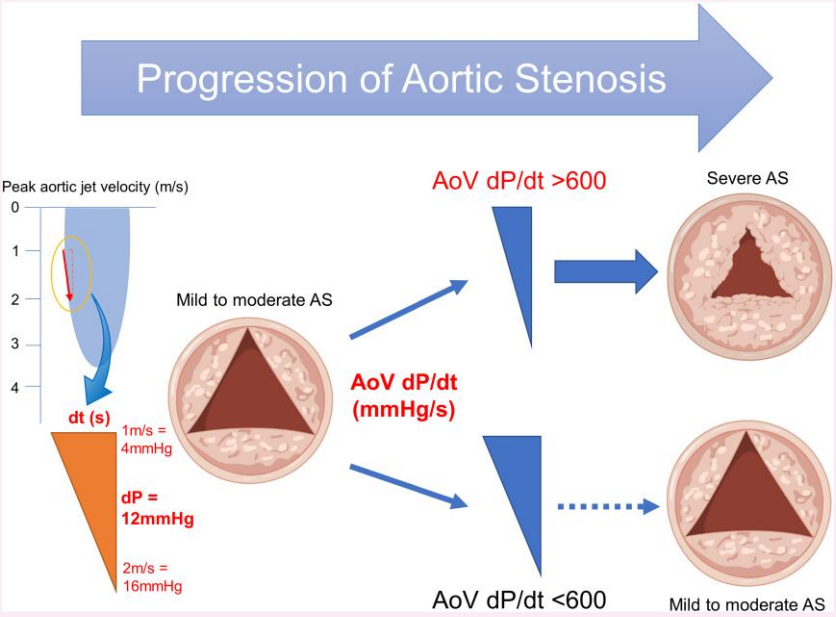
Structured Graphical Abstract

Key Question: How can be progression be predicted in patients with mild to moderate aortic stenosis (AS)?
Key Finding: Aortic valve (AoV) Doppler-derived dP/dt above 600 mmHg/s during surveillance of patients with mild to moderate AS is significantly associated with the risk of progression to the severe stage.
Take Home Message: The use of AoV Doppler-derived dP/dt may help better predict individualized risk of AS progression in patients with mild to moderate AS.



Aortic valve Doppler-derived dP/dt above 600 mmHg/s has an ability to predict the risk of progression to severe aortic stenosis in patients with mild to moderate disease. AS, aortic stenosis; AoV, aortic valve.

Keywords aortic valve • Doppler-derived dP/dt • echocardiography • aortic stenosis

Introduction

Aortic stenosis (AS) is a progressive disease that develops over decades and, once symptomatic, is associated with high morbidity and mortality.[1–3] Current guidelines do not provide a clear monitoring period for patients with mild or moderate AS, as there is inter-individual variation in the progression of these populations.[4–7] The continuous wave (CW) Doppler curve in patients with mild or moderate AS often has a rapid early peak, whereas severe AS will often display a slow acceleration with late peaking waveform.[4] Based on CW Doppler waveform of AS, we hypothesized that the acceleration of flow passing through the aortic valve (AoV) would be increased in the mild AS stage where AoV opening limitation begins. This increase of acceleration would cause continuous damage to the AoV and the difference of acceleration may explain why some patients progress faster than others at the same stage of AS. An increase in transaortic pressure gradient per unit time leads to an increase in acceleration. Therefore, the higher increase is the transaortic pressure gradient per time unit in the mild to moderate AS stage, the greater will be the progression to severe AS.

We sought to examine the association of AoV Doppler-derived dP/dt with the risk of disease progression from mild or moderate AS to severe disease.

Methods

Study population

We retrospectively included 481 patients with mild AS [aortic valve area (AVA) by continuity equation, 1.5–2.0 cm^2; peak aortic jet velocity (Vmax), 2.0–3.0 m/s], or moderate AS (AVA, 1.0–1.5 cm^2; Vmax, 3.0–4.0 m/s) and subsequently selected patients who had undergone ≥2 echocardiography examinations at ≥6 months apart during the years 2011–20. Patients with stenosis or regurgitation of at least moderate mitral or tricuspid valve and at least moderate aortic regurgitation, left ventricular (LV) dysfunction [LV ejection fraction (LVEF) < 50%], congenital heart diseases, cardiomyopathy, a permanent pacemaker, or a history of cardiac surgery were excluded.

The study protocol was approved by the institutional review board of Kangwon National University Hospital (IRB File No. KNUH-2022-10-005) involved in this research, and the need for informed consent was waived because of the retrospective nature of the study.

Clinical data

Clinical data, including the medical history and presence of risk factors, were obtained by a complete review of patient medical records. The presence of dyslipidaemia was defined by a total cholesterol >200 mg/dL or use of lipid-lowering therapy; diabetes mellitus was defined by a fasting plasma glucose >126 mg/dL, plasma glucose level >200 mg/dL at any time, or use of

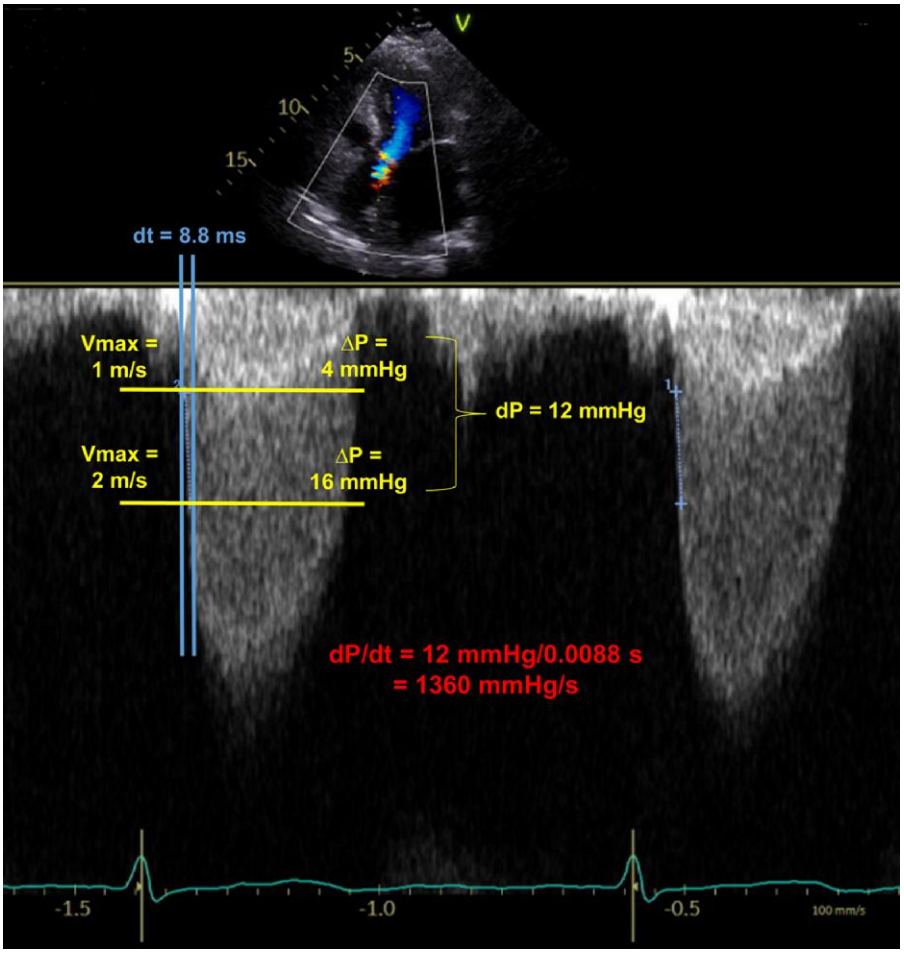


Figure 1 AoV Doppler-derived dP/dt analysis. The two points on the AoV spectrum corresponding to 1 m/s and 2 m/s were identified, and dP/dt was defined as $\Delta P/\Delta t = 16\text{-}4/\Delta t = 12$ mmHg/Δt.

anti-diabetic medication; hypertension was defined by blood pressure ≥140/90 mmHg or use of anti-hypertensive medication; and coronary artery disease (CAD) was defined by previously documented myocardial infarction or coronary artery stenosis with a lumen diameter >50% on angiography.

Echocardiography

Comprehensive transthoracic echocardiography was performed using commercially available equipment (Vivid E9 from GE Healthcare, Milwaukee, WI, USA or Acuson SC2000 from Siemens Medical Solutions, Mountain View, CA, USA). Standard M-mode, 2D, and colour Doppler imaging was performed in parasternal, suprasternal, substernal, and apical views with positional adjustment of the patient. The first and last echocardiograms collected during the study period were used to evaluate echocardiographic changes. Anatomic measurements were performed according to the European Association of Cardiovascular Imaging and the American Society of Echocardiography recommendations.[4] AoV calcification score was evaluated in four categories; calcification, thickening, localization of lesions, and leaflet mobility.[8] We assessed measurement reproducibility in 20 randomly selected cases of by repeated measurements (performed by one cardiologist and one experienced sonographer). The observers were blinded to one another's AoV calcification score measurements and the clinical endpoints.

AoV Doppler-derived dP/dt measurement

Doppler-derived dP/dt was determined as follows: the two points on the AoV spectrum corresponding to 1 m/s and 2 m/s were identified. These points corresponded to AoV pressure gradients of 4 mmHg and 16 mmHg using the modified Bernoulli equation ($P = 4v^2$). Doppler-derived dP/dt was defined as $\Delta P/\Delta t = 16\text{-}4/\Delta t = 12$ mmHg/Δt (*Figure 1*). The averages of three dP/dt measurements were determined for each patient. We measured this Doppler parameter several times repeatedly in all cases and assessed measurement reproducibility. The observers (one cardiologist and one experienced sonographer) were blinded to one another's measurements and the clinical endpoints.

Statistical analysis

Continuous variables were tested for normality using the Shapiro–Wilk test. Results are expressed as mean ± standard deviation or median (25th–75th percentile) and were compared with Student's *t*-test or the Wilcoxon rank-sum test between patients with progression to severe AS vs. no progression. Categorical variables are presented as percentages and were compared with the χ^2 test or Fisher's exact test, as appropriate.

Pearson linear correlation analysis was performed to identify the correlation between Vmax, mean pressure gradient (meanPG), AVA, and AoV calcification and AoV Doppler-derived dP/dt. Receiver operating

Table 1 Baseline characteristics

	Overall ($n = 481$)	Progression to severe AS—NO ($n = 438$)	Progression to severe AS—YES ($n = 43$)	*P-value
Clinical data				
Age, years	75 ± 9	75 ± 9	75 ± 9	0.914
Male	184 (38)	163 (37)	21 (49)	0.135
Body mass index, kg/m^2	24.4 ± 3.8	24.4 ± 3.8	24.6 ± 4.3	0.783
Initial SBP, mmHg	132 ± 20	132 ± 20	130 ± 23	0.590
Follow-up SBP, mmHg	126 ± 22	126 ± 22	126 ± 21	0.918
Initial DBP, mmHg	76 ± 12	77 ± 12	74 ± 12	0.107
Follow-up DBP, mmHg	70 ± 14	70 ± 14	68 ± 17	0.523
Cigarrete use	69 (14)	60 (14)	9 (21)	0.197
Hypertension	400 (83)	365 (83)	35 (81)	0.746
Diabetes	171 (36)	155 (35)	16 (37)	0.812
Dyslipidaemia	312 (65)	282 (64)	30 (70)	0.480
Coronary artery disease	95 (20)	88 (20)	7 (16)	0.549
Cerebrovascular accident	126 (26)	110 (25)	16 (37)	0.085
Statin use	324 (67)	290 (66)	34 (79)	0.086
Laboratory data				
Haemoglobin, g/dL	12.0 ± 2.1	12.0 ± 2.2	12.1 ± 1.8	0.847
Creatinine, mg/dL	0.8 (0.7–1.1)	0.8 (0.6–1.1)	0.9 (0.7–1.2)	0.858
Uric acid, mg/dL	5.6 ± 4.2	5.6 ± 4.4	5.7 ± 2.1	0.890
Glucose, mg/dL	129 ± 50	129 ± 49	128 ± 60	0.884
HbA1c, %	6.5 ± 1.4	6.5 ± 1.3	6.7 ± 2.0	0.342
Calcium, mg/dL	9.1 ± 4.1	9.1 ± 4.3	9.0 ± 0.5	0.797
CRP, mg/dL	0.25 (0.05–1.72)	0.23 (0.05–1.87)	0.33 (0.04–1.26)	0.064
Total cholesterol, mg/dL	162 ± 42	161 ± 41	167 ± 51	0.403
LDL, mg/dL	98 ± 38	96 ± 37	110 ± 49	**0.028**

Values are presented as mean ± standard deviation or number (%), or median (interquartile range). Bold formatting of values indicates the presence of statistical significance ($P < 0.05$).
DBP, diastolic blood pressure; HbA1c, haemoglobin A1c; RVSP, right ventricular systolic pressure; SBP, systolic blood pressure.
*P-value for no progression vs. progression to severe AS.

characteristic (ROC) curve was created to depict the predictive accuracy of the initial AoV Doppler-derived dP/dt in predicting progression to severe AS. The area under the curve (AUC) with a 95% confidence intervals (CIs) and ideal cut-off points are also shown where appropriate. Multivariable logistic regression analyses were performed to test for independent association of AoV Doppler-derived dP/dt with progression to severe AS, after adjusting for clinically relevant variables and variables with $P < 0.20$ in the univariate analysis and carefully avoiding collinearity. The adjusted variables were age, sex, body mass index, smoking status, hypertension, diabetes, dyslipidaemia, CAD, C-reactive protein (CRP), low-density lipoprotein (LDL) level, LVEF, LV global longitudinal strain (LVGLS), and initial Vmax.

$P < 0.05$ was considered statistically significant. Statistical analyses were performed using the R statistical software programme (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria) and SPSS software version 25.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

During a median follow-up period of 2.7 (interquartile range 1.5–4.5) years, 12 of 404 (3%) patients progressed from mild to severe AS, and 31 of 77 (40%) patients progressed from moderate to severe AS (see Supplementary data online, *Figure S1*). Among the 481 patients with mild to moderate AS (43 with progression to severe AS and 438 with no progression), those with progression to severe AS had a higher LDL-C level than the no progression group (110 ± 49 vs. 96 ± 37 mg/dL, $P = 0.028$). Comorbidities and laboratory findings were comparable between the groups (all $P > 0.08$, *Table 1*). Baseline characteristics of patients with mild AS and moderate AS are listed in Supplementary data online, *Tables S1* and *S2*, respectively. In the progression group of mild to moderate AS patients, the AoV calcium score was 6.7 ± 1.4, the Vmax was 3.22 ± 0.50 m/s, the meanPG was 24.6 ± 8.2 mmHg, the AVA was 1.32 ± 0.26 cm^2, the rate of progression was 0.27 (0.19–0.45) m/s/yr, and the AoV Doppler-derived dP/dt was 815 (713–1049) mmHg/s (*Table 2*). The echocardiograhic parameters at follow-up are listed in Supplementary data online, *Table S3*.

Correlation between Vmax, meanPG, AVA, and AoV calcification and AoV Doppler-derived dP/dt

Pearson linear correlation analysis suggested that Vmax and meanPG were positively correlated with AoV Doppler-derived dP/dt ($r =$ 0.813 and 0.801, $P < 0.001$ and < 0.001, respectively), while AVA was

Table 2 Echocardiographic parameters

	Overall ($n = 481$)	Progression to severe AS—NO ($n = 438$)	Progression to severe AS—YES ($n = 43$)	*P-value
Mean arterial pressure, mmHg	95 ± 13	95 ± 13	93 ± 14	0.207
Heart rate, bpm	73 ± 16	73 ± 16	73 ± 20	0.756
LVEDD, mm	48.1 ± 5.9	48.0 ± 5.9	48.5 ± 5.6	0.589
LVESD, mm	30.7 ± 5.7	30.6 ± 5.7	31.7 ± 6.1	0.269
LVMI, g/m^2	107.7 ± 47.8	107.0 ± 48.7	114.2 ± 37.6	0.351
LVEF, %	64.5 ± 9.0	64.7 ± 8.8	62.5 ± 11.3	0.124
LVGLS, %	−16.7 ± 2.8	−16.7 ± 2.8	−15.7 ± 3.0	**0.025**
SVI, mL/m^2	51.5 ± 11.4	51.5 ± 11.3	51.7 ± 12.8	0.893
Zva, mmHg·/mL·/m^2	3.0 ± 0.7	2.9 ± 0.7	3.2 ± 0.8	0.084
LAVI, mL/m^2	48.9 ± 23.1	48.8 ± 23.7	49.0 ± 16.4	0.960
E velocity, m/s	0.69 ± 0.25	0.70 ± 0.26	0.61 ± 0.16	**0.003**
A velocity, m/s	0.94 ± 0.22	0.94 ± 0.21	0.92 ± 0.26	0.517
E/e' ratio	14.1 ± 6.1	14.2 ± 6.3	13.4 ± 4.6	0.426
RVSP, mmHg	32.1 ± 10.2	32.1 ± 10.2	32.2 ± 9.9	0.919
Aortic valve calcification score	4.9 ± 1.6	4.7 ± 1.5	6.7 ± 1.4	**< 0.001**
Peak aortic jet velocity, m/s	2.51 ± 0.47	2.44 ± 0.40	3.22 ± 0.50	**< 0.001**
Mean gradient, mmHg	14.0 ± 6.8	13.0 ± 5.7	24.6 ± 8.2	**< 0.001**
Aortic valve area, cm^2	1.69 ± 0.33	1.73 ± 0.31	1.32 ± 0.26	**< 0.001**
Rate of progression, m/s/yr	0.08 (0.01–0.19)	0.06 (0.00–0.16)	0.27 (0.19–0.45)	**< 0.001**
Aortic valve dP/dt, mmHg/s	468 (373–633)	457 (363–594)	815 (713–1049)	**< 0.001**

Values are presented as mean ± standard deviation or median (interquartile range). Bold formatting of values indicates the presence of statistical significance ($P < 0.05$).
A, late diastolic mitral inflow velocity; bpm, beats per minute; E, early diastolic mitral inflow velocity; E/e', Early diastolic velocity of the mitral annulus; LAVI, left atrial volume index; LVEDD, LV end-diastolic dimension; LVESD, LV end-systolic dimension; RVSP, right ventricular systolic pressure; SVI, stroke volume index; Zva, valvulo-arterial impedance.
*P-value for no progression vs. progression to severe AS.

negatively correlated with AoV Doppler-derived dP/dt ($r = -0.548$, $P < 0.001$) (see Supplementary data online, *Figure S2*). AVA at follow-up had a weakly negative correlation with AoV Doppler-derived dP/dt ($r = -0.144$, Supplementary data online, *Figure S3A*), but AoV calcification at follow-up using the grading system[8] had a moderately positive correlation with AoV Doppler-derived dP/dt ($r = 0.537$, Supplementary data online, *Figure S3B*).

Association of AoV Doppler-derived dP/dt with progression to severe AS

In ROC analysis, AoV Doppler-derived dP/dt had a good ability to predict the risk of progression to severe AS (AUC, 0.868; $P < 0.001$), and the optimal cut-off value for AoV Doppler-derived dP/dt to predict severe AS was 600 mmHg/s (*Figure 2*). AoV Doppler-derived dP/dt above the cut-off (600 mmHg/s) was significantly associated with progression to severe AS (*Figure 3*). In the multivariable logistic regression, the initial AoV calcium score [adjusted odds ratio (aOR), 1.79; 95% CI, 1.18–2.73; $P = 0.006$] and AoV Doppler-derived dP/dt (aOR, 1.52/100 mmHg/s higher dP/dt; 95% CI, 1.10–2.05; $P = 0.012$) were associated with progression to severe AS (*Table 3*).

Reproducibility

Measurements of AoV Doppler-derived dP/dt were repeated in all patients for analysis of reproducibility. The intraclass correlation coefficients (ICCs) values for intra- and inter-observer variability of AoV Doppler-derived dP/dt measurements were 0.943 and 0.894, respectively (see Supplementary data online, *Figure S4A* and *4B*). The ICC for intra- and interobserver variability of AoV calcification score showed overall good agreement (see Supplementary data online, *Table S4*).

Discussion

The main finding of this study is that AoV Doppler-derived dP/dt above 600 mmHg/s (cut-off value from ROC curve) during surveillance of patients with mild to moderate AS is significantly associated with the risk of progression to the severe stage, independent of other potential predictors of progression. The use of AoV Doppler-derived dP/dt may help better predict individualized risk of AS progression.

Identifying individuals at increased risk of rapid AS progression remains challenging.[9] Traditional cardiovascular risk factors such as smoking, hypertension, dyslipidaemia, diabetes mellitus, and CAD have been associated with AS progression.[10,11] In addition, echocardiographic parameters, particularly initial Vmax and meanPG, are associated with risk of progression to severe AS and are crucial for the currently recommended surveillance algorithms.[4,5,7] Although these parameters are adequate for decision making in most patients, there is no single value that identifies inter-individual variability of increased risk of AS progression.[12–14] In this study, LDL level was significantly higher in patients with progression to severe AS than those with no progression, and statin use tended to be higher in the progression group. Also, the absence of follow-up LDL level after statin use makes it difficult to evaluate the degree of LDL decrease. Therefore, it is difficult to discuss the causal relationship between LDL level and the progression of AoV disease.

There is little research on the haemodynamic progression of AS using a new predictor except conventional echocardiographic

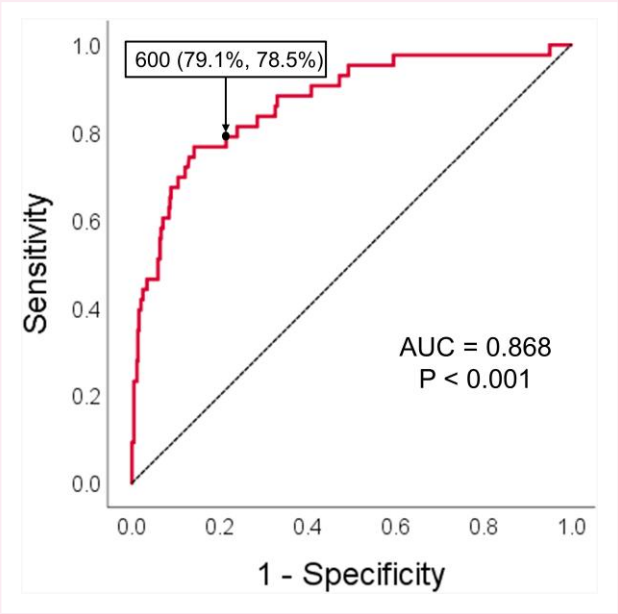


Figure 2 ROC curve depicting accuracy of initial AoV Doppler-derived dP/dt in predicting risk of progression to severe AS. The AUC is shown a 95% CI.

Table 3 Multivariable logistic regression analysis for progression to severe AS

	OR	95% CI	*P*-value
Age, years	0.98	0.93–1.05	0.603
Male	0.66	0.22–1.95	0.447
Body mass index, kg/m^2	1.07	0.95–1.21	0.249
Cigarrete use	1.34	0.36–4.97	0.667
Hypertension	1.60	0.38–6.66	0.519
Diabetes	0.97	0.36–2.66	0.960
Dyslipidaemia	1.01	0.37–2.81	0.980
Coronary artery disease	0.51	0.15–1.81	0.299
CRP, mg/dL	0.94	0.84–1.06	0.334
LDL, mg/dL	1.01	1.00–1.02	0.254
LVEF, %	0.99	0.94–1.04	0.669
LVGLS, %	0.91	0.76–1.09	0.290
Peak aortic jet velocity	1.43	0.66–3.09	0.368
Aortic valve calcification score	1.79	1.18–2.73	**0.006**
Aortic valve dP/dt, per 100 mmHg/s higher	1.52	1.10–2.05	**0.012**

Bold formatting of values indicates the presence of statistical significance ($P < 0.05$).

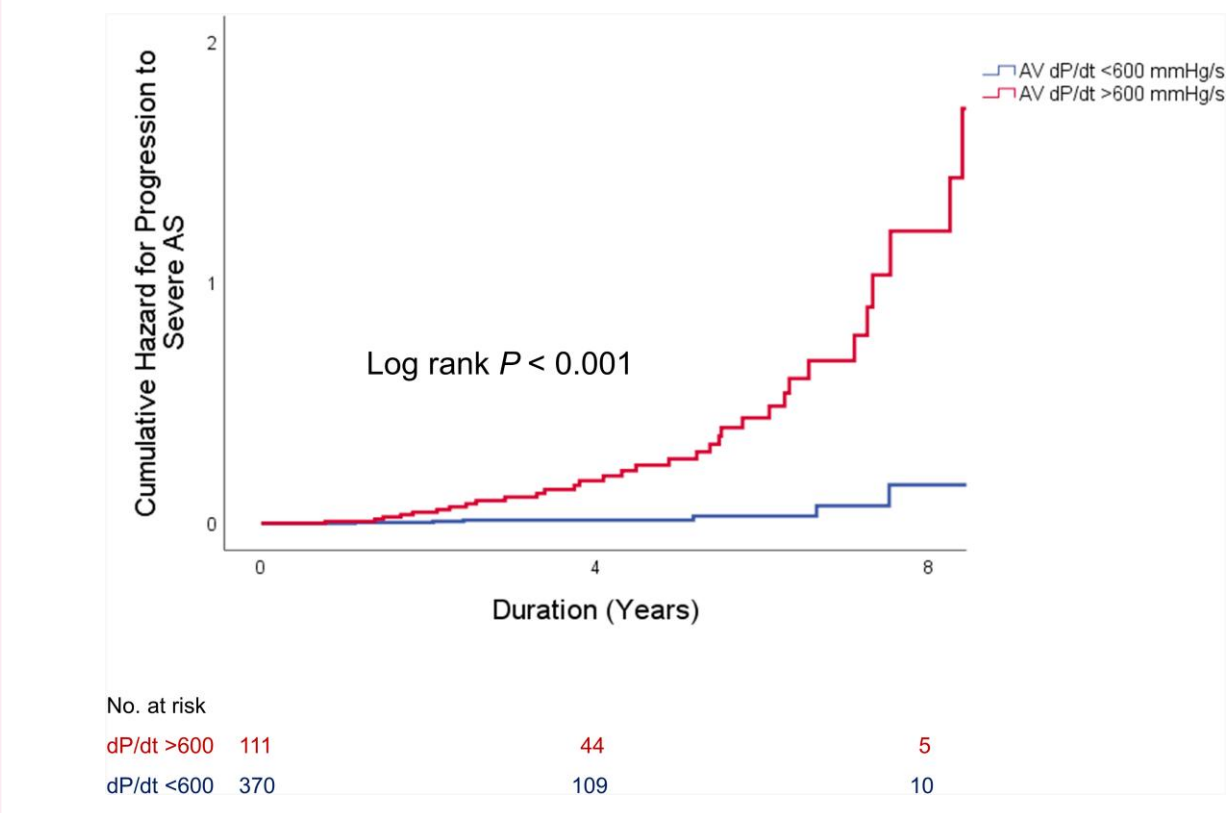


Figure 3 Progression to severe AS based on AoV Doppler-derived dP/dt.

parameters. One study suggested that initial increases in Vmax or meanPG were associated with the risk of progression to severe AS.[15] Similarly, another study showed that the rate of change in AVA could predict the haemodynamic progression of AS.[16] Using Bernoulli equation, we can know the transaortic pressure gradient at a specific velocity and its changes over time. Also, the impulse is the product of the average net force that acts on object for a certain duration. An increase in transaortic pressure gradient per unit time leads to an increase in acceleration, which causes an increase in the impulse. Hence, we conducted this study based on the assumption that a rapid increase in pressure difference per unit time causes a faster increase in blood flow velocity, which then causes further valvular damages. The present study supports this assumption through the findings that AoV Doppler-derived dP/dt has a positive correlation with AoV calcification at follow-up and that AoV Doppler-derived dP/dt above 600 mmHg/s in patients with mild to moderate AS is significantly associated with the risk of progression to severe stage.

The current surveillance schedules based solely on static measurements of AS severity may underestimate the risk of rapid progression in certain patients.[4,5,7] This study shows that patients with AoV Doppler-derived dP/dt higher than 600 mmHg/s may rapidly reach severe AS. AoV Doppler-derived dP/dt is expected to be more well reflected in the haemodynamic progression of AS because AoV dP/dt is affected by stroke volume or arterial compliance (see Supplementary data online, *Figure S5*). But in the present study, there were no signficant differences in stroke volume index or valvulo-arterial impedance between patients with progression to severe AS and those with no progression. Therefore, AoV Doppler-derived dP/dt is thought to be explained by complex mechanisms involving various factors. Overall, individualized surveillance using AoV Doppler-derived dP/dt may help identify patients in need of closer clinical follow-up.

In this study, AoV Doppler-derived dP/dt and higher AoV calcification score at baseline were significantly associated with progression to severe AS in the multivariable analyses. Additionally, the AUC suggested potentially good predictive accuracy of AoV Doppler-derived dP/dt for predicting AS progression. The term 'dP/dt' usually refers to the rate of LV pressure rise. However, we are measuring the rate of rise in the LV to aortic pressure difference, not LV pressure. The pressure difference will be affected by the systemic vascular compliance, not just LV performance. Due to the retrospective nature of the study, the effect of hypertensive medications could not be considered. Moreover, statistical power is a concern in this study, and larger-scale studies are needed to evaluate this echocardiographic parameter for independent association with progression to severe AS.

Limitations

This study has several limitations. First, the retrospective nature of the study means that other potential confounding variables not included in the analysis could have affected the results. Second, the available data did not allow for an assessment of low-gradient severe AS which may have led to an underestimation of cases progressing to the severe stage. Third, this study did not show clinical events such as cardiovascular mortality or hospitalization. However, observation of progression to severe AS is important due to its high morbidity. Fourth, valve morphology was not assessed in this study. Fifth, dP/dt is based on measuring a very short time on the Doppler tracing. The methods must include intra- and inter-observer measurement variability on a larger number of studies. Finally, this study limited the participants to a single-centre and a single ethnicity. Hence, our findings should be expanded and further verified in well-controlled prospective studies.

Conclusion

AoV Doppler-derived dP/dt above 600 mmHg/s was strongly associated with the risk of AS progression to the severe stage in patients with mild to moderate AS. This echocardiographic parameter may be a useful predictive factor for individualized risk of AS progression that can guide optimal surveillance strategies.

Supplementary data

Supplementary data are available at *European Heart Journal - Cardiovascular Imaging* online.

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Conflict of Interest: none declared.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

Authors' contributions

J.H.S. and D.R.R. designed the study and drafted the manuscript. Statistical analyses were performed by J.H.S. J.H.S., K.H.K., K.J.C., B.-K.L., B.-R.C., and D.R.R. critically revised the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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