Master's Thesis of Internal Medicine

Proteinuria is an independent predictor of rapid progression of mild to moderate aortic stenosis in patients with preserved renal function

단백뇨와 무증상 경증-중등도 대동맥판막 협착증의 급속 진행의 관계

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Abstract

Purpose: Although proteinuria is a well-known risk factor for cardiovascular disease, its relationship with the progression of aortic stenosis (AS) has not been established. Our aim was to investigate the relationship between proteinuria and AS progression.

Methods: A total of 460 patients with mild to moderate AS (defined by a peak velocity of 2.0-4.0 m/sec) without end-stage renal disease who underwent two echocardiograms at least 3 months apart were included.

Results: The progression of AS was significantly faster in patients with proteinuria than those without (108 patients vs. 352 patients; annualized reduction rate of aortic valve area (AVA), −7.7±13.5% vs. −4.5±11.6%; p=0.017). The relationship between the presence of proteinuria and the accelerated progression of AS was significant among patients with estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73 m2 (−11.0±17.5% vs. −4.2±10.0%; p <0.001), but not among those with eGFR 15-60 mL/min/1.73 m2 (−5.8±10.3 vs. −5.3±14.8%; p=0.822). When stratified by the presence of diabetes, the association of proteinuria with AS progression was only significant in patients without diabetes (−8.1±12.0% vs. −8.1±15.7%; p=0.018). Multivariable logistic regression analysis identified that the presence of proteinuria was an independent predictor of AS progression.

Conclusion: The progression of AS was accelerated in patients with mild to moderate AS and proteinuria, particularly among those with preserved renal function and no diabetes.

Key words: aortic stenosis, aortic valve area, proteinuria

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Introduction

Aortic stenosis (AS), an age-related degenerative disease, is the most common primary valve disease in developed countries, with an increasing prevalence due to ageing population [1]. To date, aortic valve (AV) replacement is the only proven therapeutic intervention to improve survival in patients with AS, and is recommended depending on AS-related symptoms or the severity of the disease [2]. With higher mortality seen among AS patients with rapid disease progression, the identification of the "rapid progression group" in mild to moderate AS patients is especially important, in order to decide on the optimal timing for intervention [3].

The clinical risk factors for rapid progression of AS are similar to those for atherosclerosis, including aging, male sex, hypertension, dyslipidemia, and smoking [4-6]. While altered calcium metabolism and hemodynamic changes in chronic kidney disease (CKD) promote the development of atherosclerosis and valvular calcification, especially in AS patients with end stage renal disease (ESRD) [7,8]. In addition, proteinuria predicted the development and progression of atherosclerotic vascular disease [9]. However, the risk of disease progression in AS patients with proteinuria and less severe kidney dysfunction is poorly described.

Therefore, this study investigated whether the presence of proteinuria in normal or mild to moderately decreased estimated glomerular filtration rate (eGFR), commonly referred to as early CKD, could predict rapid progression of mild to moderate AS. We also sought to assess the impact of diabetes on the association of proteinuria with the progression of AS.

Materials and Methods

Study design and population

This is an observational, retrospective, single-center cohort study. We collected subjects with progressive AS, who underwent more than two echocardiographic evaluations at least 3 months apart at Seoul National University Hospital (SNUH) between January 2008 and December 2017 (Figure 1).

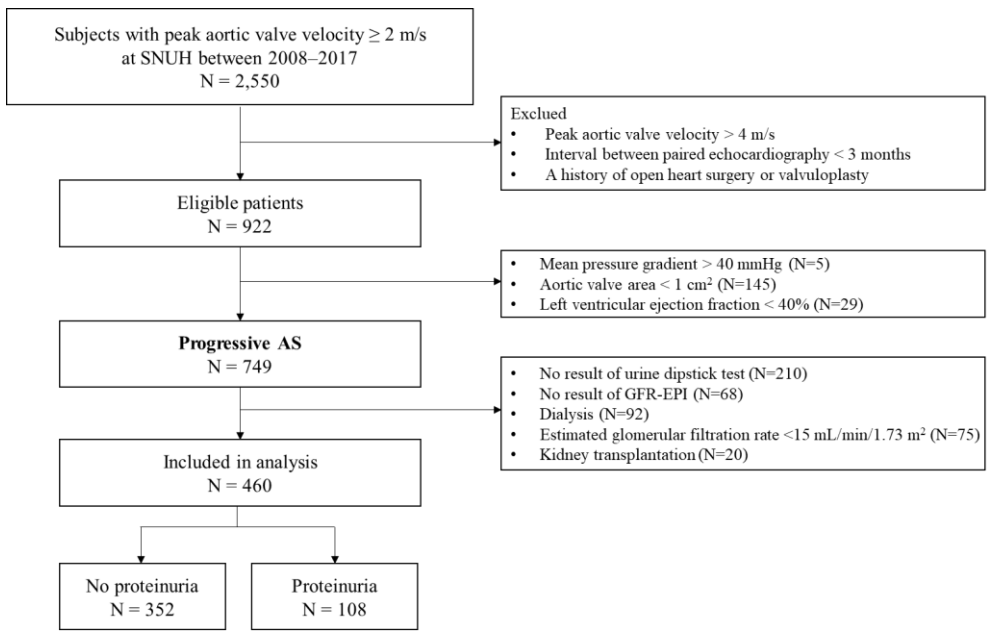

Figure 1. Flow chart of study population

Progressive AS was defined as 2–4 m/s peak aortic valve velocity (Vmax), mean transaortic pressure gradient (mPG) <40 mmHg with left ventricular ejection fraction (LVEF) >40%, and AV area (AVA) >1 cm^2 [10].

Patients were excluded if: (1) they had a history of open heart surgery, valvuloplasty, or transcatheter valve implantation before or during echocardiographic follow-up; (2) the longest interval

between the paired echocardiogram evaluations was less than 3 months; (3) no serum creatinine level and urine dipstick test (UDT) results were available; (4) other significant valvular heart disease were present; (5) there had a history of kidney transplantation; and (6) ESRD, defined as eGFR <15 mL/min/1.73 m^2 or receiving hemodialysis. After excluding those with met the exclusion criteria above, the final analysis included 460 subjects.

This study conforms to the principles of the Helsinki declaration of 1975 (revised version 2008). The study protocol was approved by the SNUH Institutional Review Board (H-1707-169-873).

Echocardiography and definition of AS progression

Echocardiograms were performed using commercially-available ultrasound and interpreted by cardiologists who specialized in echocardiography. All patients underwent comprehensive 2-dimensional and Doppler echocardiography, including pulsed-wave, continuous-wave, and color-flow imaging.

AVA was calculated by the standard continuity equation using maximum jet velocities measured at the AV and subvalvular area. The rate of AS progression was presented as the annualized reduction rate (ARR) of AVA. The ARR of AVA was calculated as follows:

$$= \left(\frac{AVA\ at\ last\ echocardiography\ [cm^2] - AVA\ at\ first\ echocardiography\ [cm^2]}{AVA\ at\ first\ echocardiography\ [cm^2]} \right) \div time\ interval\ between\ the\ two\ echocardiography\ (years) \Bigg)$$

At a mean ARR of AVA per year of 5.3%, the patients were dichotomously divided into rapid progression(ARR >5.3%, n=196) and slow progression (ARR ≤5.3%, n=264).

Measurement of proteinuria

The presence of proteinuria was defined by a 1+ or greater result on a UDT, while its absence was defined by a negative or trace result, repeated more than two times. All UDT results included were the closest in time to the last echocardiographic evaluation.

The UDT is widely used as an initial screening tool with a 95.7% sensitivity and 92.2% specificity, whereby a result of >1+ was defined as the presence of proteinuria, with urine albumin/creatinine ratio ≥300 mg/g [11]. To quantify the degree of proteinuria, spot urine protein-to-creatinine ratio in random urine samples is recommended as the optimal method for the evaluation of proteinuria or albuminuria [12]. However, the spot urine protein-to-creatinine ratio test was not mandatory in this study because it is expensive and unsuitable for screening in subjects with normal kidney function.

Measurement of kidney function

The eGFR was calculated using the CKD epidemiology collaboration (CKD-EPI) equation [13]. Kidney function was divided into 5 grades according to the K/DOQI 2012 guidelines: eGFR ≥90 mL/min/1.73 m^2, stage 1; 60-89, stage 2; 30-59, stage 3; 15-29, stage 4; and <15 or dialysis, stage 5 [14].

Covariate measurement

Clinical data including age, sex, height, weight, and comorbidities such as hypertension, diabetes, dyslipidemia, ischemic heart disease, atrial fibrillation, and stroke were obtained from a review of medical charts. Prescription data were acquired by using prescription codes from the database of electronic medical records

of SNUH. Laboratory data included results of UDT and serum levels of hemoglobin, blood urea nitrogen, creatinine, total cholesterol (high-density lipoprotein cholesterol (HDLc), low-density lipoprotein cholesterol (LDLc), triglyceride), albumin, calcium, phosphate, uric acid, B-type natriuretic peptide (BNP), and C-reactive protein (CRP). All laboratory tests included were the closest in time to the first echocardiographic evaluation.

Statistical analysis

Continuous variables were reported as mean ± standard deviation or median with interquartile ranges and categorical variables as numbers and percentages. The difference between patients with proteinuria and those without proteinuria was determined using the unpaired Student's t-test for continuous variables, and Chi-squared test for non-continuous variables. For comparison between three or more groups, the analysis of variance (AVONA) method was performed, followed by post hoc tests with the Bonferroni method to identify inter-group differences. Multivariable logistic regression analysis was performed to determine whether the presence of proteinuria is an independent predictor for rapid AS progression. Clinically relevant variables with $p < 0.1$ in the univariable regression analysis and known risk factors were included in the multivariable regression model. Results were presented as odds ratio (OR) and 95% confidence interval (CI). A $p< 0.05$ was considered statistically significant. Statistical analysis was performed using SPSS version 23 (IBM Corp, Chicago, IL, USA).

Results

Baseline characteristics of study population

Among a total of 460 patients included in the final analysis, 108 patients had proteinuria. The mean age was 69.6±11.6 years, and 70.6% patients were older than 65 years. Of the study population, 50.4% were male. The etiology of AS was degenerative stenosis (82.4%), bicuspid stenosis (9.8%), and rheumatic AV (7.8%). The median time interval between paired echocardiographic evaluations was 30 months (range, 4–104 months).

The baseline characteristics of the study population and comparisons according to the presence or absence of proteinuria are shown in Table 1. The mean follow-up duration was shorter in patients with proteinuria (median 28 months) than those without (median 34 months) ($p=0.014$). Patients with positive UDT had significantly higher values of microalbumin-to-creatinine ratio and protein-to-creatinine ratio than those with negative test (All $p<0.001$, Table 2). Compared to patients without proteinuria, those with proteinuria did not differ in terms of sex and the etiology of AS; however, they were older ($p=0.015$) and had higher prevalence of diabetes ($p<0.001$), atrial fibrillation ($p=0.004$), and stroke ($p=0.006$). Patients with proteinuria had more prescriptions for diuretics ($p=0.035$). In baseline laboratory tests, patients with proteinuria had a higher level of uric acid ($p=0.007$) and BNP ($p=0.002$), and lower levels of total cholesterol ($p=0.041$), HDLc ($p=0.027$), serum albumin ($p<0.001$), and eGFR ($p<0.001$). The patients with proteinuria had lower value of Vmax ($p=0.027$) and LV outflow tract diameter ($p=0.035$), and higher value of pulmonary artery systolic pressure ($p<0.001$) and LA volume index

(p=0.031), but similar AVA and LVEF compared to those without proteinuria.

Table 1. Baseline characteristics of the study population according to the presence or absence of proteinuria

Variable	Total (n=460)	Proteinuria (n = 108)	No proteinuria (n = 352)	p value
Clinical data				
Age, years	69.3 ± 11.6	71.7 ± 11.3	68.6 ± 11.7	0.015
Male, n (%)	232 (50.4%)	50 (46.3%)	182 (51.7%)	0.383
Body mass index, kg/m^2	24.2 ± 3.66	24.0 ± 4.18	24.4 ± 3.49	0.590
Systolic blood pressure, mmHg	131.7 ± 17.9	133.2 ± 21.1	131.2 ± 16.8	0.309
Diastolic blood pressure, mmHg	69.3 ± 11.2	68.6 ± 13.1	69.5 ± 10.6	0.446
Heart rate, bpm	69.2 ± 14.0	69.2 ± 13.8	69.1 ± 14.1	0.953
Hypertension, n (%)	243 (52.8%)	59 (54.6%)	184 (52.2%)	0.750
Dyslipidemia, n (%)	160 (34.8%)	35 (32.4%)	125 (35.6%)	0.633
Diabetes, n (%)	141 (30.7%)	47 (43.5%)	94 (26.7%)	0.001
Ischemic heart disease, n (%)	178 (38.7%)	46 (42.6%)	132 (37.5%)	0.402
Atrial fibrillation, n (%)	101 (22.0%)	35 (32.4%)	66 (18.8%)	0.004
Stroke, n (%)	92 (20.0%)	32 (29.6%)	60 (17.0%)	0.006
Medication, n (%)				
ACE inhibitors or ARB	197 (42.8%)	44 (40.7%)	153 (43.5%)	0.697
β-blockers	168 (36.5%)	44 (40.7%)	124 (35.2%)	0.354
Calcium channel blockers	237 (51.5%)	64 (59.3%)	173 (49.1%)	0.084
Diuretics	234 (50.9%)	65 (60.2%)	169 (48.0%)	0.035
Spironolactone	77 (16.7%)	24 (22.2%)	53 (15.1%)	0.110
Statin	260 (56.5%)	68 (63.0%)	192 (54.5%)	0.152
Laboratory data				
Hemoglobin, g/dL	12.8 ± 3.82	12.5 ± 5.47	12.9 ± 3.14	0.378
Total cholesterol, mg/dL	163.8 ± 37.1	157.4 ± 34.7	165.8 ± 37.7	0.041
Triglycerides, mg/dL	126.7 ± 71.5	138.5 ± 97.1	123.3 ± 62.2	0.085
LDL cholesterol, mg/dL	96.8 ± 31.6	95.1 ± 32.7	97.3 ± 31.4	0.689
HDL cholesterol, mg/dL	48.9 ± 14.5	45.9 ± 12.9	49.8 ± 14.8	0.027

Serum albumin, g/dL	4.02 ± 0.50	3.81 ± 0.56	4.09 ± 0.46	<0.001
Uric acid, mg/dL	5.62 ± 1.71	6.00 ± 1.97	5.50 ± 1.61	0.007
Calcium, mg/dL	9.24 ± 4.48	8.90 ± 0.56	9.34 ± 5.15	0.387
Phosphate, mg/dL	3.43 ± 0.55	3.38 ± 0.64	3.44 ± 0.51	0.349
Alkaline phosphatase, IU/L	71.3 ± 31.2	76.9 ± 37.0	69.6 ± 29.1	0.033
eGFR, ml/min/1.73 m^2	67.6 ± 22.6	55.2 ± 25.5	71.4 ± 20.2	<0.001
B-type natriuretic peptide, pg/mL[a]	395.1 ± 688.3	738.9 ± 1043.3	274.8 ± 454.8	0.002
C-reactive protein, mg/dL[a]	1.52 ± 4.12	2.14 ± 4.47	1.32 ± 3.98	0.091
Echocardiographic data				
Bicuspid aortic valve, n (%)	45 (9.8%)	8 (7.4%)	37 (10.5%)	0.445
Rheumatic aortic valve, % n (%)	36 (7.8%)	10 (9.3%)	36 (7.8%)	0.668
Peak aortic jet velocity, m/s	2.66 ± 0.48	2.58 ± 0.47	2.69 ± 0.48	0.027
Peak subvalular jet velocity, m/s	1.15 ± 0.26	1.18 ± 0.30	1.14 ± 0.24	0.107
Mean transvalvular gradient, mmHg	16.1 ± 6.62	15.0 ± 6.46	16.4 ± 6.65	0.051
Aortic valve area, cm^2	1.52 ± 0.41	1.55 ± 0.37	1.51 ± 0.42	0.398
LV outflow tract diameter, mm	21.0 ± 2.13	20.7 ± 1.84	21.1 ± 2.19	0.035
LV ejection fraction, %	61.7 ± 6.11	60.8 ± 6.70	62.0 ± 5.91	0.087
PASP, mmHg[a]	34.9 ± 8.17	38.3 ± 9.22	33.9 ± 7.58	<0.001
LA volume index, mL/m^{2a}	50.9 ± 29.3	56.8 ± 31.0	49.1 ± 28.5	0.031
Follow-up duration, months (Q1–Q3)	30 (17–56)	28 (15–47)	34 (18–58)	0.014

Values of continuous variable are mean ± SD.

[a]The number of case included in the analysis was is 227, 434, 374, and 369, respectively.

Abbreviations; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; LV, left ventricular; PASP, pulmonary artery systolic pressure; LA, left atrial.

Table 2. The value of microalbumin-to-creatinine ratio and protein-to--creatinine ratio according to results of urine dipstick test

	Number of subject	Mean value	SD	p value
Microalbumin/Creatinine ratio (random urine)				
Dipstick positive	64	0.78	1.395	<0.001
Dipstick negative	163	0.07	0.216	
Protein/Creatinine ratio (random urine)				
Dipstick positive	61	1.65	2.808	<0.001
Dipstick negative	108	0.34	0756	

Association between the presence of proteinuria and progression of AS

During a median follow-up of 30 months, the mean AVA decreased from 1.52 to 1.33 cm^2, and mPG increased from 16.1 to 20.9 mmHg. The mean reduction rate of AVA was 5.28% per year. The ARR distribution of follow-up duration was shown in Figure 2. The follow-up echocardiography data are shown in Table 3. As comparing with baseline, the values of Vmax and mPG were higher at follow-up.

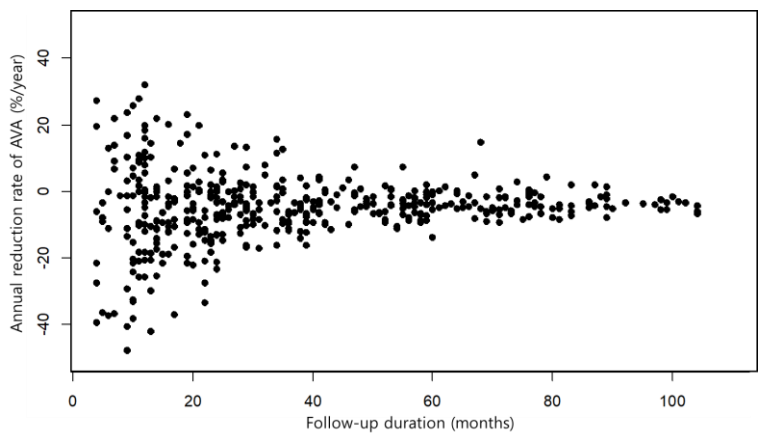

Figure 2. Annual reduction rate distribution of AVA over follow-up duration. –

Table 3. Follow-up echocardiography data of the study population according to the presence or absence of proteinuria

Echocardiographic data	Total (n = 460)	Proteinuria (n = 108)	No proteinuria (n = 352)	p value
Peak aortic jet velocity, m/s	2.98 ± 0.73	3.03 ± 0.75	2.80 ± 0.63	0.004
Peak subvalular jet velocity, m/s	1.07 ± 0.23	1.08 ± 0.22	1.06 ± 0.26	0.515
Mean transvalvular gradient, mmHg	20.9 ± 12.3	21.9 ± 12.9	17.4 ± 9.60	<0.001
Aortic valve area, cm^2	1.33 ± 0.43	1.32 ± 0.43	1.33 ± 0.45	0.794
Left ventricular ejection fraction, %	60.3 ± 7.57	58.2 ± 9.13	60.9 ± 6.92	0.001

Values are mean ± SD.

The mean ARR of AVR was significantly higher in patients with proteinuria than those without among grades 1-4 of kidney functions (p=0.017, Figure 4).

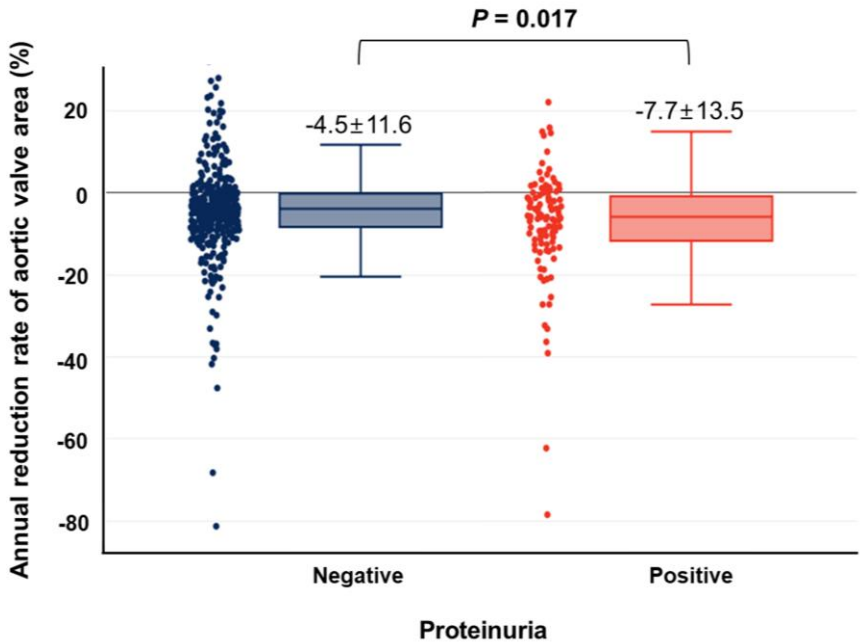

Figure 3. Box plots demonstrating the relationship between the presence proteinuria detected by urine dipstick test and the annualized reduction rate in aortic valve area. The numbers above the boxes represent mean value±standard deviation of the annualized reduction rate.

There was no significant difference in the ARR of AVA (%) between CKD grades: stage 1 (−6.8±14.0); stage 2 (−4.4±10.2); stage 3 (−5.5±13.5); and stage 4 (−5.6±10.9) (AVONA, p=0.705). However, in a subgroup analysis divided by eGFR 60 mL/min/1.73 m2, the presence of proteinuria had a significant association with accelerated AS progression in patients with eGFR ≥60 mL/min/1.73 m2 (p <0.001, Figure 4B), while no difference was seen in those with eGFR <60 mL/min/1.73 m2 (p=0.822, Figure 4A).

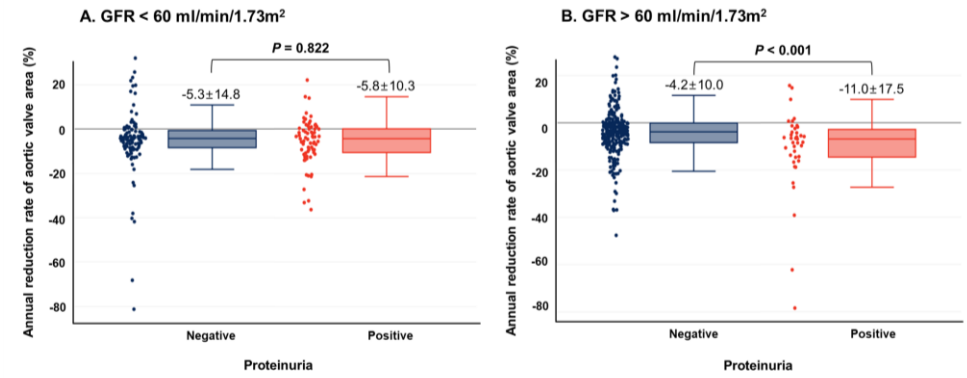

Figure 4. Box plots demonstrating the relationship between the presence proteinuria detected by urine dipstick test and the annualized reduction rate in aortic valve area, according to estimated glomerular filtration rate (eGFR).

At a mean ARR of AVA per year of 5.3%, the patients were dichotomously divided into rapid (ARR >5.3%, n=196) and slow progression (ARR ≤5.3%, n=264). The variables examined by univariate and multivariate analyses for the prediction of rapid progression of AS are listed in Table 4. After adjustment by univariate factors with p <0.10 and traditional risk factors of AS progression, multivariable analysis demonstrated that rapid progression of AS was independently associated with the presence of proteinuria (adjusted OR 1.88, 95% CI 1.08–3.32, p=0.027).

Table 4. Association between proteinuria and rapid progression of aortic valve stenosis in univariable and multivariable logistic regression models

Variables	Univariable analysis			Multivariable analysis*		
	OR	95% CI	p value	OR	95% CI	p value
Proteinuria	**1.89**	**1.22–2.92**	**0.004**	**1.88**	**1.08–3.32**	**0.027**
Age	1.03	1.00–1.04	0.004	1.03	1.00–1.06	0.021
Male	0.68	0.47–0.98	0.041	0.62	0.37–1.04	0.069

Systolic blood pressure	1.00	0.99–1.01	0.617			
Diastolic blood pressure	0.99	0.98–1.01	0.928			
Hypertension	1.26	0.87–1.83	0.222			
Dyslipidemia	0.99	0.67–1.46	0.973			
Diabetes	2.02	1.41–3.15	<0.001	2.36	1.44–3.86	<0.001
Ischemic heart disease	1.13	0.77–1.64	0.541			
Atrial fibrillation	1.43	0.92–2.23	0.114	1.43	0.81–2.53	0.215
Stroke	2.02	1.27–3.21	0.003	1.66	0.95–2.88	0.070
Total cholesterol	1.00	0.99–1.00	0.607	1.00	0.99–1.00	0.372
Triglycerides	1.00	0.99–1.00	0.114			
HDL cholesterol	1.00	0.98–1.01	0.555	1.01	0.99–1.02	0.384
LDL cholesterol	0.99	0.99–1.00	0.102			
Serum albumin	0.62	0.42–0.90	0.011	1.03	0.59–1.82	0.908
Alkaline phosphatase	1.00	1.00–1.01	0.197	1.00	0.99–1.01	0.552
Calcium	1.02	0.96–1.08	0.477			
Phosphate	0.75	0.52–1.07	0.113			
Uric acid	0.99	0.89–1.11	0.888			
eGFR, categorical	0.89	0.56–1.43	0.642	0.52	0.26–1.04	0.064
B-type natriuretic peptide	1.00	1.00-1.00	0.212			
C-reactive protein	1.03	0.98-1.08	0.211			
Bicuspid aortic valve	0.52	0.26–1.01	0.053	1.03	0.40–2.64	0.949
LVOT diameter	0.94	0.86–1.03	0.167	0.89	0.77–1.03	0.114
Peak aortic jet velocity	1.09	0.74–1.60	0.676			
mPG	1.00	0.97–1.03	0.956			
PASP, mmHg	1.02	0.99–1.05	0.156			
LA volume index	1.00	1.00–1.00	0.844			
Aortic valve area	2.04	1.29–3.25	0.002	2.35	1.21–4.57	0.027

*Adjusted by age, sex, diabetes, stroke, atrial fibrillation, HDL, Total cholesterol, APL, LVOT diameter, serum albumin, bicuspid valve, eGFR, and aortic valve area.
Abbreviations; OR, odds ratio; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; eGFR, estimated glomerular filtration rate; LVOT, left ventricular outflow track; mPG, mean transortic pressure gradient; PASP, pulmonary artery systolic pressure; LA, left atrial.

Impact of proteinuria on progression of AS in patients with diabetes

Overall, the ARR of AVA was faster in patients with diabetes. The ARR of AVA was significantly faster in patients with proteinuria than those without proteinuria (p=0.018, Figure 5B) among individuals without diabetes. However, the impact of proteinuria on AVA reduction rate was not significant among those with diabetes (Figure 5A).

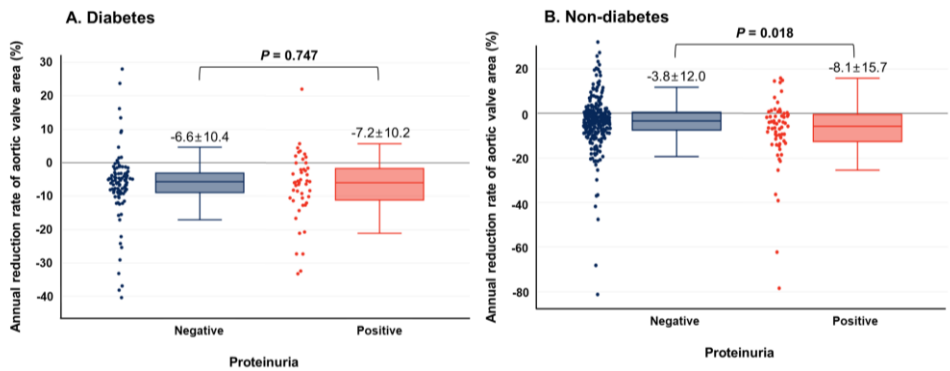

Figure 5. Box plots demonstrating the relationship between the presence proteinuria detected by urine dipstick test and the annualized reduction rate in aortic valve area, according to presence of diabetes.

Subgroup analysis stratified statin use

When we stratified patients according to statin use, 260 (56.5%) were statin user and 200 (43.5%) were statin non-users (Table 5). Among statin users, 68 patients (26.2%) had proteinuria and 192 patients (73.8%) had not. In this subgroup of statin users, the ARR of AVA was numerically greater in patients with proteinuria than those without (p=0.058). In the subgroup of statin non-users, the reduction rate of AVA was also higher in patients with proteinuria than those without (p=0.099). When comparing 2 subgroups, statin users had a lower reduction rate in AVA than statin non-user,

regardless of the presence (p=0.371) or absence of proteinuria (p=0.500).

Table 5. The relationship between proteinuria and annualized reduction rate in aortic valve area according to use of statin.

	Statin user (n = 260)			Statin non-user (n = 200)		
	Proteinuria (n = 68)	No proteinuria (n = 192)	p value	Proteinuria (n = 40)	No proteinuria (n = 160)	p value
Annualized reduction rate in AVA, %	-6.81 ± 8.86	-4.15 ± 10.3	0.058	-9.23 ± 19.1	-4.99 ± 13.1	0.099

Values are expressed as mean ± SD.

Abbreviations; AVA, aortic valve area.

Discussion

In this retrospective cohort study, the presence of proteinuria, as detected by urine dipstick test, was significantly associated with accelerated progression of AS among patients with mild to moderate AS. The impact of proteinuria on AS progression was greater in patients with eGFR ≥60 mL/min/1.73 m2 than those with eGFR <60 mL/min/1.73 m2. Moreover, proteinuria among patients without diabetes significantly accelerated AS disease progression. However, there was no significant difference accruing to the presence of proteinuria among patients with diabetes.

Effects of proteinuria on rapid progression of AS

Proteinuria is a risk factor for cardiovascular disease and atherosclerosis progression [17–19]. In the present study, patients with proteinuria had a 1.9–fold higher risk for rapid AS progression

(≥5.39% reduction rate of AVA per year), even after adjustment for important confounders. Considering that most of the protein detected by urine dipstick test is albumin, our finding extends the evidence for albuminuria as an independent risk factor for accelerated AS progression.

Given the strong relationship between albuminuria and kidney disease as well as coronary vascular disease, the K/DOQI 2012 guidelines recommends using albuminuria rather than total protein levels to classify CKD stages, as well as using the GFR category and routinely screen for proteinuria in patients at higher risk of CKD, such as those with diabetes, hypertension, older age, etc [16]. Albuminuria is not only an indicator of nephropathy in type 1 diabetes, but also a predictor of cardiovascular mortality in non-diabetics or healthy subjects [20,21].

Albuminuria reflects a more generalized vascular process, which affects the glomeruli for nephropathy, the retina for diabetic retinopathy, and the intima of large vessels for atherosclerosis; this explains the mechanism for increased cardiovascular mortality with albuminuria [22,21,23]. In addition, convincing histopathological and clinical evidences suggested that the progression of AS and atherosclerotic process share common pathophysiology, including lipoprotein deposition, inflammation, and calcification of valves and arterial walls [24]. Deposition of lipoprotein such as apoB and 4-hydroxynonenal-modified LDLc, and enhanced inflammatory activity, represented by increased T-lymphocytes and macrophages with HLA-DR expression, were observed in the vicinity of calcium deposits on degenerative AV [25]. Therefore, we hypothesize that albuminuria is a marker of accumulation of lipids, accelerated calcification, and increased inflammatory activity,

all of which play key roles in the disease progression of AS [23,22]. When multivariate analysis using Cox proportional hazards model due to variability of the follow-up period of the subjects, they also showed that proteinuria increases the risk of AS progression persistently (table not shown).

Early chronic kidney disease and rapid progression of AS

CKD is a poor prognostic factor for AS and other cardiovascular diseases, including vascular calcification and atherosclerosis, as well as ESRD hemodialysis patients [9,10,26]. In elderly patients with AS, severe kidney dysfunction is an independent predictor of rapid increase in mPG and hemodynamic progression [27]. However, they do not imply a relationship between the CKD grade and disease progression rate of AS. In our study, there was no significant difference in annualized reduction rate of AVA in patients with AS accruing to CKD grades 1 to 4. Of note, among patients with CKD grades 1 to 4, individuals with proteinuria had a significantly higher annualized reduction rate of AVA than those without proteinuria. These findings suggest that proteinuria can predict AS progression earlier than kidney function impairment. Moreover, because proteinuria in normal or mildly decreased kidney function (i.e., early CKD) is more prevalent than ESRD [28], our study has a greater implication in terms of preventative treatment strategy of AS, following earlier identification of the rapid progression group.

Effects of proteinuria and diabetes on progression of AS

In our study, the impact of proteinuria on the disease progression rate of AS was confined to non-diabetic patients. This suggested

that the pathogenesis of proteinuria in diabetes and AS may be different, resulting in different effects of angiotensin-converting enzyme (ACE) inhibitors on disease progression. ACE, which is associated with angiotensin II enzyme and lipid deposition, is present in calcified AV, suggesting the potential role of renin-angiotensin in the pathogenesis of AS [29]. Many researchers have therefore investigated the effects of ACE inhibitors on AS progression, with conflicting results. Specifically, several previous retrospective studies have shown that the ACE inhibitors and angiotensin receptor blockers (ARB) might be realted with calcium accumulation on AV [30,31]. However, most prospective studies have suggested that statins – not ACE inhibitors – could delay the disease progression of AS [32-34]. Further investigations are clearly required to better define the potential role ACE inhibitors or ARB in reducing proteinuria as a means to prevent progression of AS.

Study limitations

In addition to the limitations inherent to a retrospective single-center study design with a relatively small sample size, the following limitations should be considered when interpreting our findings. First, we calculated the AVA by using the standard continuity equation and used it as a representative value of AS progression, rather than the AV Vmax and mPG, which more accurately reflect the hemodynamics of AS. However, the standard continuity equation is clinically convenient as an evaluation of AVA; in addition, most previous studies on AS have adopted it for AVA evaluation.

Second, we did not provide the data regarding the relationship

between the degree of proteinuria and reduction rate of AVA, since quantitative measures of proteinuria were available in only small number of patients. Although our finding demonstrated that the urine dipstick test results might well reflect microalbumin-to-creatinine ratio and protein-to-creatinine ratio (Table 2), we should acknowledge that the dipstick test is semi-quantitative.

Finally, the findings of our subgroup analysis by statin use should be interpreted with caution because of the small number of subjects in each subgroup, likely leading to an underpowered statistical analysis. Although our study suggests the possibility that the benefit of statin therapy on AS progression may differ according to the presence or absence of proteinuria, future studies are required to shed more light on this issue, particularly considering previous negative clinical trials [35-37]. Despite the above limitations, our findings demonstrated the significant association between the presence of proteinuria and rapid AS progression, suggesting a potential role of proteinuria as a sensitive marker for AS progression.

Conclusion

Proteinuria detected by urine dipstick test was an independent risk factor for rapid progression of mild to moderate AS. The relationship between proteinuria and AS progression was more obvious among patients with preserved renal function and those without diabetes. Proteinuria in mild to moderate AS may be helpful in identifying patients at high-risk of accelerated disease progression, for whom more frequent clinical and echocardiographic surveillance must be considered.

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국문 초록

연구 목적: 단백뇨가 심혈관질환의 불량한 예후와 관련이 있음에 대하여 널리 잘 알려져 있다. 그에 반해 대동맥 판막 협착증의 진행과 단백뇨와의 관계에 대한 연구는 부족하다. 본 연구는 단백뇨와 대동맥 판막 협착증의 진행에 관련성에 대한 관계를 분석함을 목적으로 한다.

연구 방법: 2007년부터 2017년까지 서울대학교 병원 심장초음파 검사실에서 확인된 경증-중증도 대동맥 판막 협착증 환자 460명을 대상으로, 최소 3개월 이상의 간격으로 시행된 심장초음파 검사 결과를 비교하여 대동맥 판막 면적의 변화 정도를 통하여 대동맥 판막 협착증의 진행 정도를 평가하여 단백뇨 유무에 따른 차이를 비교한다.

연구 결과: 요시험지검사를 통하여 단백뇨가 확인된 108명의 환자와 352명의 단백뇨가 확인되지 않은 환자를 비교하였을 때, 단백뇨가 동반된 환자군에서 년간 대동맥 판막 면적 감소 속도가 현저하게 빨랐다. (−7.7±13.5% vs. −4.5±11.6%; p=0.017). 단백뇨와 대동맥 판막증의 빠른 진행과의 관계는 사구체여과율 ≥60 mL/min/1.73m^2 인 환자에서 더욱 뚜렷하게 확인되으나 (−11.0±17.5% vs. −4.2±10.0%; p <0.001), 사구체 여과율이 15−60 mL/min/1.73 m^{2}인 환자에서는 두 군간의 통계적인 차이를 보이지 못했다 (−5.8±10.3 vs. −5.3±14.8%; p=0.822). 당뇨병의 동반 유무에 따른 하위 분석에서, 당뇨병이 없는 환자에서만 단백뇨와 대동맥 판막의 빠른 진행과의 연관성이 통계적으로 유의했다 (−8.1±12.0% vs. −8.1±15.7%; p=0.018). 다중 변수 로지스틱 회귀 분석을 통해 단백뇨가 대동맥판막증의 빠른 진행을 예측하는 독립적인 인자임을 확인했다.

결론: 경증-중증도 대동맥판막 협착증 환자에서 대동맥판막 협착증의 진행은 요시험지 검사를 통하여 1+ 이상의 단백뇨가 확인된 환자, 특히 신장 기능이 유지되고 당뇨병이 없는 환자에서 가속화 되었다.

주요어: 대동맥판막협착증, 단백뇨, 당뇨

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