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ORIGINAL PAPER

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

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## Abstract

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 (detected by urine dipstick test) and AS progression (assessed by the annualized reduction rate of aortic valve area [AVA]). A total of 460 patients with mild to moderate AS (defined by a peak velocity of 2.0–4.0 m/s) without end-stage renal disease who underwent two echocardiograms at least 3 months apart were included. The progression of AS was significantly faster in patients with proteinuria than those without (108 patients vs. 352 patients; annualized reduction rate of AVA, $-7.7 \pm 13.5\%$ vs. $-4.5 \pm 11.6\%$; $p = 0.017$). The relationship between the presence of proteinuria and the accelerated progression of AS was significant among patients with estimated glomerular filtration rate (eGFR) $\geq 60$ mL/min/1.73 $m^2$ ($-11.0 \pm 17.5\%$ vs. $-4.2 \pm 10.0\%$; $p < 0.001$), but not among those with eGFR 15–60 mL/min/1.73 $m^2$ ($-5.8 \pm 10.3$ vs. $-5.3 \pm 14.8\%$; $p = 0.822$). When stratified by the presence of diabetes, the association of proteinuria with AS progression was only significant in patients without diabetes ($-8.1 \pm 12.0\%$ vs. $-8.1 \pm 15.7\%$; $p = 0.018$). Multivariable logistic regression analysis identified that the presence of proteinuria was an independent predictor of AS progression. 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.

**Keywords** Aortic stenosis · Aortic valve area · Proteinuria

## 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

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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.

$$\text{Annualized reduction rate of AVA (\%)} = \left( \frac{\text{AVA at last echocardiography}\left[\text{cm}^2\right] - \text{AVA at first echocardiography}\left[\text{cm}^2\right]}{\text{AVA at first echocardiography}\left[\text{cm}^2\right]} \right) \Big/ \text{time interval between the two echocardiography (years)}$$

## Materials and methods

### Study design and population

This is an observational, retrospective, single-center cohort study. The cohort consisted of 460 patients with progressive AS, who underwent more than two echocardiographic evaluations at Seoul National University Hospital (SNUH) between January 2008 and December 2017.

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.

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 two-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:

### 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 five 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) and R programming version 3.2.4 (http://www.R-project.org; The R Foundation for Statistical Computing, Vienna, Austria).

## 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 $p < 0.001$, Supplementary Table 1). 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.

### 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 follow-up echocardiography data are shown in Table 2. As comparing with baseline, the values of Vmax and mPG were higher at follow-up.

The mean ARR of AVA was significantly higher in patients with proteinuria than those without among grades 1–4 of kidney functions ($p = 0.017$, Fig. 1). 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 $m^2$, the presence of proteinuria had a significant association with accelerated AS progression in patients with eGFR ≥ 60 mL/min/1.73 $m^2$ ($p < 0.001$, Fig. 2b), while no difference was seen in those with eGFR < 60 mL/min/1.73 $m^2$ ($p = 0.822$, Fig. 2a).

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 3. 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 2.25, 95% CI 1.25–4.05, $p = 0.007$).

**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 are mean ± SD or number of patients (%) where appropriate

*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

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

**Table 2** 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

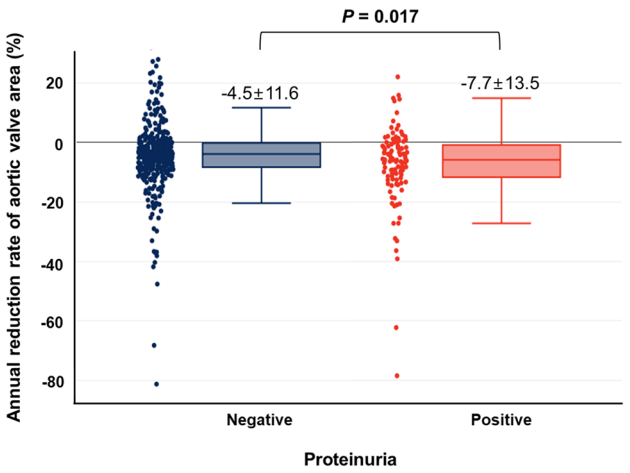


**Fig. 1** Box plots demonstrating the relationship between the presence proteinuria detected by urine dipstick test and the annualized reduction rate in aortic valve area. The numbers above the boxes represent mean value ± standard deviation of the annualized reduction rate

## 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, Fig. 3b) among individuals without diabetes. However, the impact of proteinuria on AVA reduction rate was not significant among those with diabetes (Fig. 3a).

## 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 (Supplementary Table 1). 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 two subgroups, statin users had a lower reduction

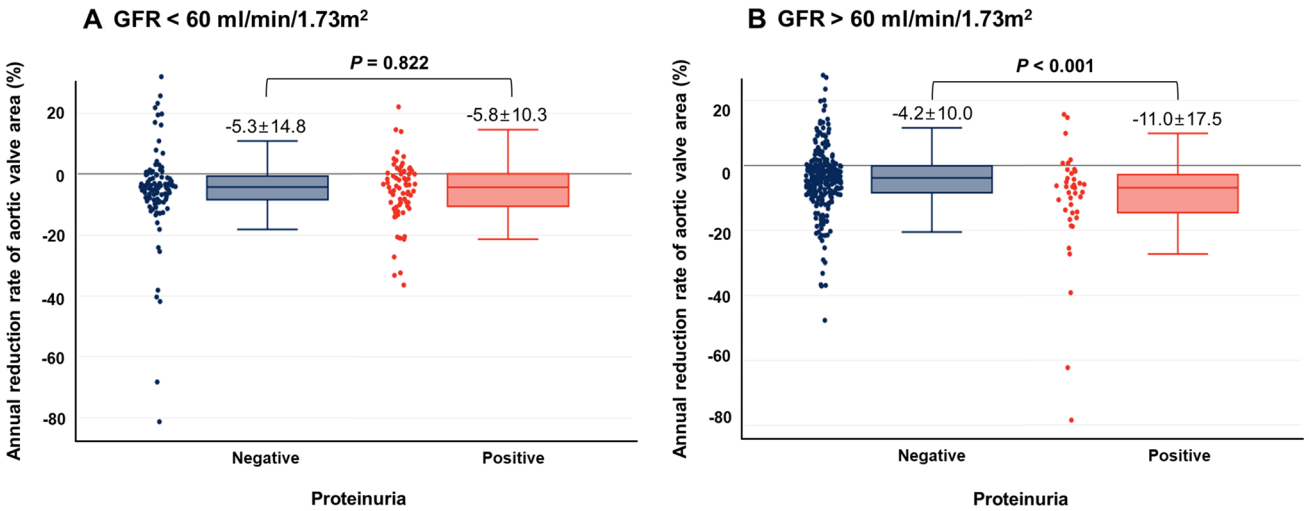


**Fig. 2** Box plots demonstrating the relationship between the presence proteinuria detected by urine dipstick test and the annualized reduction rate in aortic valve area, according to estimated glomerular filtration rate (eGFR)

**Table 3** Univariable and multivariable analyses of the association between proteinuria and progression of aortic valve stenosis

| Variables | Univariable analysis | | | Multivariable analysis* | | |
|---|---|---|---|---|---|---|
| | OR | 95% CI | p value | OR | 95% CI | p value |
| Proteinuria | **1.89** | **1.22–2.92** | **0.004** | **2.25** | **1.25–4.05** | **0.007** |
| Age | 1.03 | 1.00–1.04 | 0.004 | 1.04 | 1.01–3.81 | 0.013 |
| Male | 0.68 | 0.47–0.98 | 0.041 | 0.63 | 0.37–1.05 | 0.078 |
| 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 | 2.37 | 1.45–3.87 | < 0.001 |
| Ischemic heart disease | 1.13 | 0.77–1.64 | 0.541 | | | |
| Atrial fibrillation | 1.43 | 0.92–2.23 | 0.114 | 1.44 | 0.81–2.56 | 0.208 |
| Stroke | 2.02 | 1.27–3.21 | 0.003 | 1.65 | 0.95–2.87 | 0.075 |
| Total cholesterol | 1.00 | 0.99–1.00 | 0.607 | 1.00 | 0.99–1.00 | 0.491 |
| Triglycerides | 1.00 | 0.99–1.00 | 0.114 | | | |
| HDL cholesterol | 1.00 | 0.98–1.01 | 0.555 | 1.00 | 0.99–1.02 | 0.581 |
| LDL cholesterol | 0.99 | 0.99–1.00 | 0.102 | | | |
| Serum albumin | 0.62 | 0.42–0.90 | 0.011 | 0.98 | 0.56–1.72 | 0.935 |
| Alkaline phosphatase | 1.00 | 1.00–1.01 | 0.197 | 1.00 | 0.99–1.01 | 0.460 |
| 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 | 1.00 | 0.99–1.00 | 0.858 | 1.02 | 1.00–1.03 | 0.018 |
| 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 | 0.98 | 0.38–2.53 | 0.973 |
| LVOT diameter | 0.94 | 0.86–1.03 | 0.167 | 0.90 | 0.77–1.04 | 0.152 |
| 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 | 0.012 |

*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

*Adjusted by age, sex, diabetes, stroke, atrial fibrillation, HDL, Total cholesterol, APL, LVOT diameter, serum albumin, bicuspid valve, eGFR, and aortic valve area

rate in AVA than statin non-user, regardless of the presence (p = 0.371) or absence of proteinuria (p = 0.500).

## Discussion

In this retrospective cohort study, the presence of proteinuria, as detected by UDT, 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 $m^2$ than those with eGFR < 60 mL/min/1.73 $m^2$. 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 progression of AS

Proteinuria is a risk factor for cardiovascular disease and atherosclerosis progression [15–17]. In the present study, patients with proteinuria had a 2.3-fold higher risk for rapid AS progression (≥ 5.39% reduction rate of AVA per year), even after adjustment for important confounders.

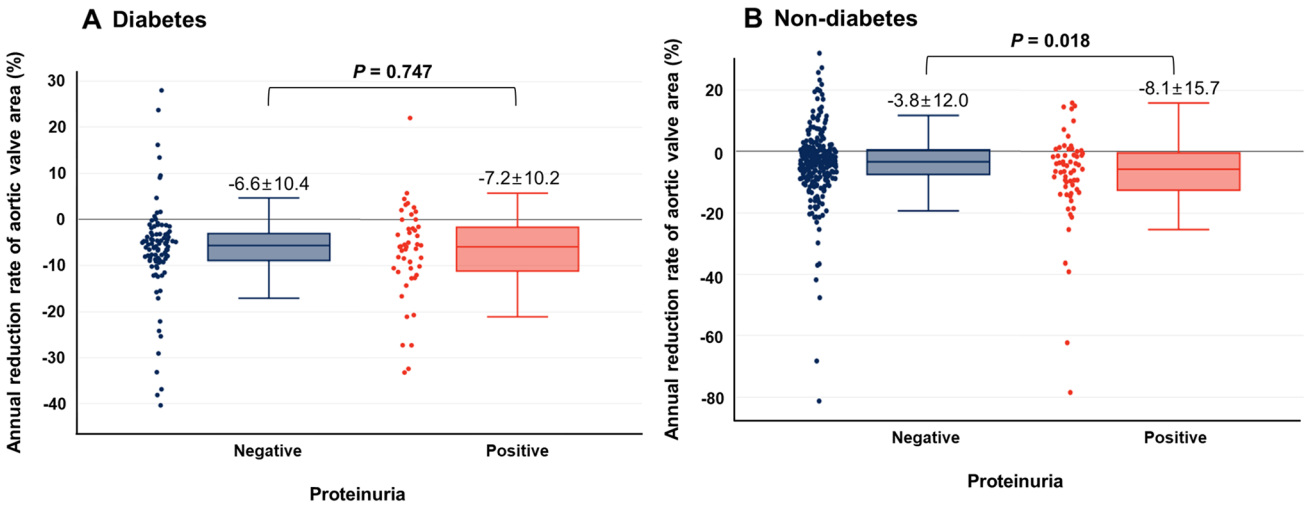


**Fig. 3** Box plots demonstrating the relationship between the presence proteinuria detected by urine dipstick test and the annualized reduction rate in aortic valve area, according to presence of diabetes

Considering that most of the protein detected by UDT 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. [14]. 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 [18, 19].

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 [19–21]. 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 [22]. 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 [23]. 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 [20, 21].

## Early chronic kidney disease and progression of AS

CKD is a poor prognostic factor for AS and other cardiovascular diseases, including vascular calcification and atherosclerosis [8, 24]. In elderly patients with AS, severe kidney dysfunction is an independent predictor of rapid increase in mPG and hemodynamic progression [25]. 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 ARR of AVA in patients with AS accruing to CKD grades 1–4. Of note, among patients with CKD grades 1–4, individuals with proteinuria had a significantly higher ARR of AVA than those without. 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 [26], 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 [27]. 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 related with calcium accumulation on AV [28, 29]. However, most prospective studies have suggested that statins—not ACE inhibitors—could delay the disease progression of AS [30–32].

### 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 UDT results might well reflect quantitative measures of proteinuria, 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 [33, 34].

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 UDT 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.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

## References

1. Coffey S, Cox B, Williams MJ (2014) The prevalence, incidence, progression, and risks of aortic valve sclerosis: a systematic review and meta-analysis. J Am Coll Cardiol 63(25 Pt A):2852–2861. https://doi.org/10.1016/j.jacc.2014.04.018
2. Murphy ES, Lawson RM, Starr A, Rahimtoola SH (1981) Severe aortic stenosis in patients 60 years of age or older: left ventricular function and 10-year survival after valve replacement. Circulation 64(2 Pt 2):184–188
3. Rosenhek R, Klaar U, Schemper M, Scholten C, Heger M, Gabriel H, Binder T, Maurer G, Baumgartner H (2004) Mild and moderate aortic stenosis. Natural history and risk stratification by echocardiography. Eur Heart J 25(3):199–205. https://doi.org/10.1016/j.ehj.2003.12.002
4. Stewart BF, Siscovick D, Lind BK, Gardin JM, Gottdiener JS, Smith VE, Kitzman DW, Otto CM (1997) Clinical factors associated with calcific aortic valve disease. Cardiovascular Health Study. J Am Coll Cardiol 29(3):630–634
5. Palta S, Pai AM, Gill KS, Pai RG (2000) New insights into the progression of aortic stenosis—implications for secondary prevention. Circulation 101(21):2497–2502
6. Tastet L, Capoulade R, Clavel MA, Larose E, Shen M, Dahou A, Arsenault M, Mathieu P, Bedard E, Dumesnil JG, Tremblay A, Bosse Y, Despres JP, Pibarot P (2017) Systolic hypertension and progression of aortic valve calcification in patients with aortic stenosis: results from the PROGRESSA study. Eur Heart J Cardiovasc Imaging 18(1):70–78. https://doi.org/10.1093/ehjci/jew013
7. London GM, Pannier B, Marchais SJ, Guerin AP (2000) Calcification of the aortic valve in the dialyzed patient. J Am Soc Nephrol 11(4):778–783
8. Leskinen Y, Paana T, Saha H, Groundstroem K, Lehtimaki T, Kilpinen S, Huhtala H, Airaksinen J (2009) Valvular calcification and its relationship to atherosclerosis in chronic kidney disease. J Heart Valve Dis 18(4):429–438
9. Miettinen H, Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M (1996) Proteinuria predicts stroke and other atherosclerotic vascular disease events in nondiabetic and non-insulin-dependent diabetic subjects. Stroke 27(11):2033–2039
10. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, O'Gara PT, Ruiz CE, Skubas NJ, Sorajja P, Sundt TM 3rd, Thomas JD, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Creager MA, Curtis LH, DeMets D, Guyton RA, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Stevenson WG, Yancy CW, American College of C, American College of Cardiology/American Heart A, American Heart A (2014) 2014 AHA/ACC guideline 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. J Thorac Cardiovasc Surg 148(1):e1–e132. https://doi.org/10.1016/j.jtcvs.2014.05.014
11. Lim D, Lee DY, Cho SH, Kim OZ, Cho SW, An SK, Kim HW, Moon KH, Lee MH, Kim B (2014) Diagnostic accuracy of urine dipstick for proteinuria in older outpatients. Kidney Res Clin Pract 33(4):199–203. https://doi.org/10.1016/j.krcp.2014.10.003

12. Kristal B, Shasha SM, Labin L, Cohen A (1988) Estimation of quantitative proteinuria by using the protein-creatinine ratio in random urine samples. Am J Nephrol 8(3):198–203
13. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, Ckd EPI (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150(9):604–612
14. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, Kurella Tamura M, Feldman HI (2014) KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis 63(5):713–735. https://doi.org/10.1053/j.ajkd.2014.01.416
15. Chiu YW, Adler SG, Budoff MJ, Takasu J, Ashai J, Mehrotra R (2010) Coronary artery calcification and mortality in diabetic patients with proteinuria. Kidney Int 77(12):1107–1114. https://doi.org/10.1038/ki.2010.70
16. DeFilippis AP, Kramer HJ, Katz R, Wong ND, Bertoni AG, Carr J, Budoff MJ, Blumenthal RS, Nasir K (2010) Association between coronary artery calcification progression and microalbuminuria the MESA study. Jacc-Cardiovasc Imag 3(6):595–604. https://doi.org/10.1016/j.jcmg.2010.01.008
17. Park HE, Heo NJ, Kim M, Choi SY (2013) Significance of microalbuminuria in relation to subclinical coronary atherosclerosis in asymptomatic nonhypertensive, nondiabetic subjects. J Korean Med Sci 28(3):409–414. https://doi.org/10.3346/jkms.2013.28.3.409
18. Dinneen SF, Gerstein HC (1997) The association of microalbuminuria and mortality in non-insulin-dependent diabetes mellitus. A systematic overview of the literature. Arch Intern Med 157(13):1413–1418
19. van der Toll A, Van Biesen W, De Groote G, Verbeke P, Vermeiren F, Eeckhaut K, Vanholder R (2013) Microalbuminuria is more consistent in the presence of cardiovascular risk factors. J Nephrol 26(3):580–585. https://doi.org/10.5301/jn.5000194
20. Jensen JS, Borch-Johnsen K, Jensen G, Feldt-Rasmussen B (1995) Microalbuminuria reflects a generalized transvascular albumin leakiness in clinically healthy subjects. Clin Sci 88(6):629–633
21. Deckert T, Feldt-Rasmussen B, Borch-Johnsen K, Jensen T, Kofoed-Enevoldsen A (1989) Albuminuria reflects widespread vascular damage. Diabetologia 32(4):219–226
22. Freeman RV, Otto CM (2005) Spectrum of calcific aortic valve disease: pathogenesis, disease progression, and treatment strategies. Circulation 111(24):3316–3326. https://doi.org/10.1161/CIRCULATIONAHA.104.486738
23. Olsson M, Thyberg J, Nilsson J (1999) Presence of oxidized low density lipoprotein in nonrheumatic stenotic aortic valves. Arterioscler Thromb Vasc Biol 19(5):1218–1222
24. Ohara T, Hashimoto Y, Matsumura A, Suzuki M, Isobe M (2005) Accelerated progression and morbidity in patients with aortic stenosis on chronic dialysis. Circ J 69(12):1535–1539
25. Kearney LG, Ord M, Buxton BF, Matalanis G, Patel SK, Burrell LM, Srivastava PM (2013) Progression of aortic stenosis in elderly patients over long-term follow up. Int J Cardiol 167(4):1226–1231. https://doi.org/10.1016/j.ijcard.2012.03.139
26. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS (2007) Prevalence of chronic kidney disease in the United States. JAMA 298(17):2038–2047. https://doi.org/10.1001/jama.298.17.2038
27. O'Brien KD, Shavelle DM, Caulfield MT, McDonald TO, Olin-Lewis K, Otto CM, Probstfield JL (2002) Association of angiotensin-converting enzyme with low-density lipoprotein in aortic valvular lesions and in human plasma. Circulation 106(17):2224–2230
28. Cote N, Couture C, Pibarot P, Despres JP, Mathieu P (2011) Angiotensin receptor blockers are associated with a lower remodelling score of stenotic aortic valves. Eur J Clin Invest 41(11):1172–1179. https://doi.org/10.1111/j.1365-2362.2011.02522.x
29. O'Brien KD, Probstfield JL, Caulfield MT, Nasir K, Takasu J, Shavelle DM, Wu AH, Zhao XQ, Budoff MJ (2005) Angiotensin-converting enzyme inhibitors and change in aortic valve calcium. Arch Intern Med 165(8):858–862. https://doi.org/10.1001/archinte.165.8.858
30. Ardehali R, Leeper NJ, Wilson AM, Heidenreich PA (2012) The effect of angiotensin-converting enzyme inhibitors and statins on the progression of aortic sclerosis and mortality. J Heart Valve Dis 21(3):337–343
31. Rosenhek R, Rader F, Loho N, Gabriel H, Heger M, Klaar U, Schemper M, Binder T, Maurer G, Baumgartner H (2004) Statins but not angiotensin-converting enzyme inhibitors delay progression of aortic stenosis. Circulation 110(10):1291–1295. https://doi.org/10.1161/01.CIR.0000140723.15274.53
32. Jimenez-Candil J, Bermejo J, Yotti R, Cortina C, Moreno M, Cantalapiedra JL, Garcia-Fernandez MA (2005) Effects of angiotensin converting enzyme inhibitors in hypertensive patients with aortic valve stenosis: a drug withdrawal study. Heart 91(10):1311–1318. https://doi.org/10.1136/hrt.2004.047233
33. Rossebo AB, Pedersen TR, Boman K, Brudi P, Chambers JB, Egstrup K, Gerdts E, Gohlke-Barwolf C, Holme I, Kesaniemi YA, Malbecq W, Nienaber CA, Ray S, Skjaerpe T, Wachtell K, Willenheimer R, Investigators S (2008) Intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis. N Engl J Med 359(13):1343–1356. https://doi.org/10.1056/NEJMoa0804602
34. Chan KL, Teo K, Dumesnil JG, Ni A, Tam J, Investigators A (2010) Effect of Lipid lowering with rosuvastatin on progression of aortic stenosis: results of the aortic stenosis progression observation: measuring effects of rosuvastatin (ASTRONOMER) trial. Circulation 121(2):306–314. https://doi.org/10.1161/CIRCULATIONAHA.109.900027