ORIGINAL ARTICLE

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Chronic kidney disease is a key risk factor for aortic stenosis progression

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ABSTRACT

Background. Rapid progression of aortic stenosis (AS) has been observed in patients undergoing dialysis, but existing cross-sectional evidence is contradictory in non-dialysis-dependent chronic kidney disease (CKD). The present study sought to evaluate whether CKD is associated with the progression of AS over time in a large cohort of patients with AS.

Methods. We retrospectively studied all consecutive patients diagnosed with AS [peak aortic jet velocity (Vmax) ≥2.5 m/s] and left ventricular ejection fraction ≥50% in the echocardiography laboratories of two tertiary centers between 2000 and 2018. The estimated glomerular filtration rate (eGFR) (mL/min/1.73 m^2) was calculated from serum creatinine values. Patients were divided into five CKD stages according to the baseline eGFR. Annual rates of change in the aortic valve area (AVA) were determined by a linear mixed-effects model.

Results. Among the 647 patients included, 261 (40%) had CKD. After a median follow-up of 2.9 (interquartile range 1.8–4.8) years, the mean overall rate of change in AVA was –0.077 (95% confidence interval –0.082; –0.073) cm^2/year. There was an inverse relationship between the progression rate and kidney function. The more severe the CKD stage, the greater the AVA narrowing ($P < .001$). By multivariable linear regression analysis, the eGFR was also negatively associated ($P < .001$) with AS progression. An eGFR strata below 45 mL/min/1.73 m^2 was associated with higher odds of rapid progression of AS than normal kidney function. During the clinical follow-up, event-free survival (patients free of aortic valve replacement or death) decreased as CKD progressed. Rapid progression of AS in patients with kidney dysfunction was associated with worse outcomes.

Conclusions. Patients with CKD exhibit more rapid progression of AS over time and require close monitoring. The link between kidney dysfunction and rapid progression of AS is still unknown and requires further research.

Keywords: aortic stenosis, aortic valve replacement, chronic kidney disease, mortality, progression

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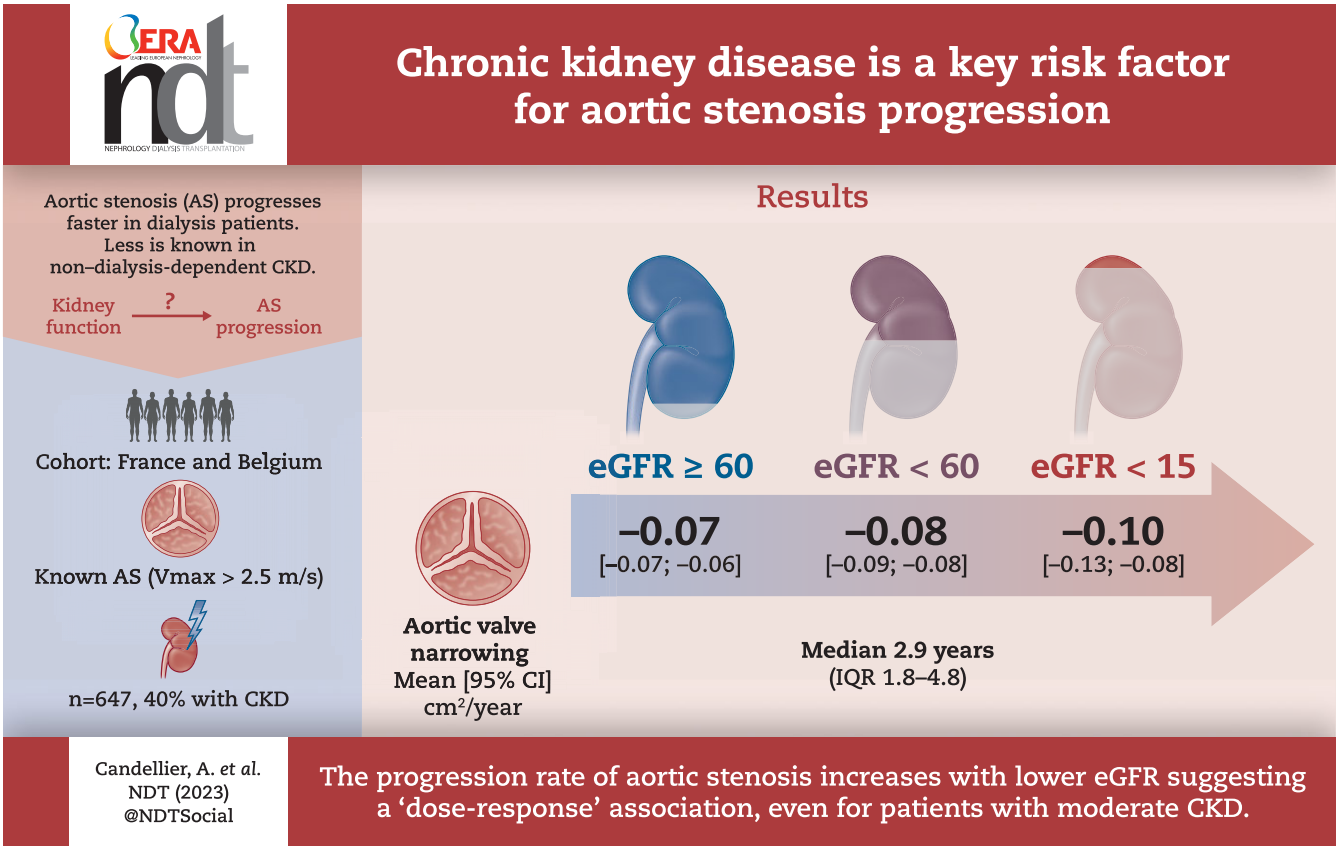
GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What was known:

- Aortic stenosis (AS) progresses faster in dialysis patients. This evidence is contradictory in non–dialysis-dependent chronic kidney disease (CKD). Knowing whether kidney dysfunction worsens AS progression is important for improving the management of patients with AS and CKD and could help physicians in the monitoring and decision-making process.

This study adds:

- This study of a large cohort of patients with AS and varying degrees of CKD sheds new light on the impact of kidney dysfunction among non-dialysis patients on AS progression. The progression rate increases with lower estimated glomerular filtration rate, suggesting a "dose–response" association, even for patients with moderate CKD.

Potential impact:

- Patients with kidney dysfunction should be closely monitored and those with rapid progression seriously considered for aortic valve replacement decision making. It is, therefore, important to include a nephrologist as an integral component of the heart–kidney team in the management, even for patients with mild to moderate CKD.

INTRODUCTION

Aortic stenosis (AS) is the most common valvular heart disease, especially in the elderly and patients with chronic kidney disease (CKD) [1]. CKD is among the fastest-growing chronic diseases, making it an important public health problem [2, 3]. Several studies have suggested a greater risk of cardiovascular mortality for patients with AS and concomitant CKD than those with normal kidney function [4–6]. However, little is known about the impact of kidney dysfunction on the progression of AS. Although it is well established that aortic valve calcification is frequent and AS progression is faster for patients requiring dialysis than those with normal kidney function [7–9], the conflicting results for patients with moderate or severe increases in serum creatinine levels [10–12] raise questions concerning the potential risk of rapid AS progression attributed to kidney dysfunction. Nevertheless, mineral and hemodynamic disturbances induced by CKD contribute to the pathophysiology of cardiovascular calcification, and increase morbidity and mortality [13]. Knowing whether there is an association between kidney dysfunction and AS progression is important for improving the management of patients with AS and CKD and could help physicians in the monitoring and decision-making process.

Our objectives were, therefore, to (i) analyze the relationship between kidney function and AS progression over time, as assessed by transthoracic echocardiogram (TTE), and (ii) evaluate the impact of both CKD and CKD-associated rapid AS progression on survival in a large cohort of patients with AS.

MATERIALS AND METHODS

Patient population

The flow chart of the study is presented in Supplementary data, Fig. S1. Between 2000 and 2018, we identified 4247 consecutive patients ≥18 years of age diagnosed with AS [aortic leaflet calcification and a peak aortic jet velocity (Vmax) ≥2.5 m/s] in the echocardiography laboratories of one French (Amiens) and one Belgian (Brussels) tertiary center. Patients with prosthetic valves, mitral stenosis, congenital heart disease, supravalvular or subvalvular AS, or dynamic left ventricular outflow tract (LVOT) obstruction were not included in the electronic database. For the present study, we retrospectively identified all patients who had two or more TTE studies at least 1 year apart. Exclusion criteria were at baseline or follow-up: (i) a left ventricular ejection fraction (LVEF) <50%; (ii) aortic and/or mitral regurgitation of more than mild severity; (iii) kidney graft recipient, patients experiencing dialysis or kidney transplantation between the two TTE studies, patients without available serum creatinine measurements at baseline or with time interval between the first echo and baseline serum creatinine >2 months, patients with estimated glomerular filtration rate (eGFR) decrease >25% from baseline at the enrollment (two outpatient serum creatinine levels separated by at least 3 months were evaluated to exclude them) or primary hyperparathyroidism; and (iv) patients who denied authorization for participation. The study was approved by an independent ethics committee and conducted in accordance with institutional policies, national legal requirements and the revised principles of the Declaration of Helsinki.

Study parameters

Clinical and demographic baseline characteristics were collected. Comorbid conditions were scored using the Charlson comorbidity index [14] and adjusted for age and kidney function. The updated European System for Cardiac Operative Risk Evaluation (EuroSCORE II), which is a well-established cardiac surgery risk-scoring tool, was used for estimating operative mortality for each patient [15]. This score takes into account patient-, cardiac- and operative-related factors. All TTEs were performed by trained cardiologists using commercially available ultrasound systems. Careful measurements of the LVOT diameter in a zoomed cine loop of the parasternal long-axis view in early systole at the level of aortic cusp insertion were systematically performed and repeated at least three to five times. We used the same value of LVOT diameter for each serial echocardiography. Aortic flow was systematically recorded by continuous-wave Doppler in several views (apical five-chamber, right parasternal, suprasternal and epigastric). The view identifying the highest velocities was used to calculate the aortic velocity–time integral (VTI) and to determine the Vmax. Three consecutive measurements in this view for patients in sinus rhythm or five for patients in atrial fibrillation were averaged [16]. The aortic valve area (AVA) was calculated using the continuity equation. The left ventricular outflow tract velocity time integral (LVOT VTI) was recorded using pulsed-wave Doppler from the apical five-chamber view, with the sample volume positioned approximately 5 mm proximal to the aortic valve. The LVEF was calculated using Simpson's biplane method [17]. AS severity stage was categorized regarding AVA (mild >1.5 cm^2, moderate 1.0–1.5 cm^2 and severe <1.0 cm^2) as defined by the current valvular guidelines [18]. Serum creatinine measurements were standardized to the reference method of isotope-dilution mass spectrometry in each study center. The eGFR was determined using the 2009 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) [19] equation based on serum creatinine values at baseline echocardiography. CKD stages were defined according to Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [20] as follows: stage 3a (eGFR 45–59 mL/min/1.73 m^2), stage 3b (30–44 mL/min/1.73 m^2), stage 4 (eGFR 15–29 mL/min/1.73 m^2) and stage 5 (eGFR <15 mL/min/1.73 m^2 or dialysis). Patients with an eGFR ≥60 mL/min/1.73 m^2 were used as the reference group. Among dialysis patients, the eGFR was assumed to be 5 mL/min/1.73 m^2. A serum creatinine value was also collected at the final TTE. To examine the robustness of our findings, regardless of the method of estimating kidney function, we performed several analyses using a GFR estimated by the Modification of Diet in Renal Disease (MDRD) Study equation [21] and the 2021 CKD-EPI equation [22].

AS progression

Follow-up echocardiograms were performed during a consultation that included a patient interview and clinical examination according to current recommendations. We used the data from the latest available TTE for analysis. Concerning AS progression, we assessed various AS parameters: AVA, mean pressure gradient and Vmax. The last TTE was considered as time 0 and previous measurement as negative. As previously described [23], we defined rapid progression as annualized progression of AVA above the median value for patients in this cohort. Patients were further categorized into two subgroups (nonrapid progression vs rapid progression) according to an annualized decrease in AVA ≤0.07 or >0.07 cm^2/year. Progression in AS severity stage was defined as any step-ups in AS severity including mild AS that progressed to either moderate to severe, or moderate AS that progressed to severe.

Statistical analysis

SPSS version 25 software (IBM, Armonk, NY, USA) was used for statistical analysis. The linear mixed model, as well as the associated figures, was generated using R software version 4.0.5 (R Foundation for Statistical Computing, Vienna, Austria) through the RStudio interface, version 2022.07.1. There were no missing data for the variables of interest. Continuous variables are expressed as the means (± standard deviation) or medians [interquartile range (IQR)] and categorical variables as frequencies (percentages) and counts. The relationship between baseline continuous variables and those of the groups was explored by one-way ANOVA (for normally distributed variables) or Kruskal–Wallis tests (for non-normally distributed variables). Pearson's χ^2 statistic or Fisher's exact test were used to examine the association between baseline categorical variables and those of the groups. Individual differences were compared using Mann–Whitney U tests (with a Bonferroni correction) and Tukey tests for normally distributed data. For comparisons between baseline and follow-up values, paired Student's *t*-test, McNemar's test or Wilcoxon's signed-rank sum test were used, as appropriate. The annualized progression rate of AVA was determined using the linear mixed-effect model based on repeated measurements of AVA from subsequent TTEs of the same subject. A quadratic effect of time was entered into this model

Table 1: Baseline demographic, clinical and biological characteristics of the study population with aortic stenosis according to CKD stage.

Variable	eGFR, mL/min/1.73 m²					P-value
	≥60 (*n* = 386)	45–59 (*n* = 125)	30–44 (*n* = 90)	15–29 (*n* = 26)	<15 (*n* = 20)	
Demographics, baseline data and symptoms						
Age (years)	72.7 ± 12.5	78.4 ± 7.6***	78.9 ± 7.9***	80.0 ± 6.7***	72.6 ± 10.8**	<.001
Male sex (*n*, %)	218 (56.5)	56 (44.8)*	48 (53.3)	16 (61.5)	14 (70.0)	.10
Body mass index (kg/m²)	27.2 ± 4.9	27.8 ± 5.0	28.7 ± 4.9	27.4 ± 4.2	27.2 ± 6.8	.13
Body surface area (m²)	1.86 ± 0.2	1.84 ± 0.2	1.88 ± 0.2	1.85 ± 0.2	1.87 ± 0.3	.70
Systolic blood pressure (mmHg)	139 ± 19	143 ± 19	143 ± 22	141 ± 19	143 ± 20	.16
Diastolic blood pressure (mmHg)	76 ± 11	77 ± 13	74 ± 12	71 ± 12	72 ± 17	.04
Heart rate (beats/min)	71 ± 13	70 ± 13	74 ± 16	70 ± 13	72 ± 10	.30
NYHA (*n*, %)						.04
1–2	350 (90.7)	109 (87.2)	77 (85.6)	19 (73.1)**	16 (80.0)*	
3–4	36 (9.3)	16 (12.8)	13 (14.4)	7 (26.9)	4 (20.0)	
Medical history and risk factors						
Hypertension (*n*, %)	290 (75.1)	106 (84.8)*	83 (92.2)**	24 (92.3)**	19 (95.0)***	<.001
Diabetes mellitus (*n*, %)	101 (26.2)	35 (28.0)	34 (37.8)*	15 (57.7)***	8 (40.0)*	<.01
Dyslipidemia (*n*, %)	213 (55.2)	60 (48.0)*	58 (64.4)	18 (69.2)	14 (70.0)	.06
Smoking history (*n*, %)	82 (21.2)	15 (12.0)	14 (15.6)	4 (15.4)	7 (35.0)	.05
Coronary artery disease (*n*, %)	138 (35.8)	40 (32.0)	48 (53.3)**	16 (61.5)**	11 (55.0)**	.001
Prior myocardial infarction (*n*, %)	36 (9.3)	7 (5.6)	13 (14.4)	5 (19.2)	4 (20.0)	.05
Prior atrial fibrillation (*n*, %)	79 (20.5)	35 (28.0)	29 (31.5)	10 (38.5)	6 (30.0)	.06
Severe lung disease (*n*, %)	61 (15.8)	14 (11.2)	17 (18.9)	2 (7.7)	3 (15.0)	.44
Charlson comorbidity index (without age and kidney function)	1.62 ± 1.6	2.05 ± 1.7	2.29 ± 1.5***	3.23 ± 1.7**	2.5 ± 1.91	<.001
Euroscore II	1.73 ± 1.7	2.46 ± 1.9**	3.86 ± 3.0***	4.33 ± 3.4***	3.21 ± 2.2*	<.001
Chronic medication (*n*, %)						
ACE-I/ARB	173 (44.8)	63 (50.4)	63 (70.0)	19 (73.1)***	5 (25.0)***	<.001
β-blockers	162 (42.0)	61 (48.8)	39 (43.3)	17 (65.4)	11 (55.0)	.12
Calcium channel blockers	105 (27.2)	35 (28.0)	30 (33.3)	9 (34.5)	5 (25.0)	.74
Statins	195 (50.5)	65 (52.0)	54 (60.0)	21 (80.8)***	9 (45.0)	.02
Aspirin	166 (43.0)	58 (46.4)	49 (54.4)**	18 (69.2)***	12 (60.0)**	.03
Vitamin K antagonists	51 (13.2)	25 (20.0)*	21 (23.3)*	6 (23.1)*	6 (30.0)*	.04
Baseline kidney function						
Serum creatinine (µmol/L)	74.8 ± 14.5	102.0 ± 15.2***	133.0 ± 21.0***	191.6 ± 37.8***	668.4 ± 237.3***	<.001
eGFR (mL/min/1.73 m²)	79.9 ± 13.5	52.4 ± 4.4***	38.9 ± 4.0***	25.7 ± 3.5***	6.3 ± 3.2***	<.001
BUN (mmol/L)	6.15 ± 1.9	8.19 ± 3.2***	10.7 ± 3.4***	15.5 ± 6.7***	25.8 ± 5.9***	<.001

Continuous variables are expressed as mean ± 1 SD and categorical variables as counts and percentages.
NYHA: New York Heart Association class; ACE-I/ARB: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; BUN: blood urea nitrogen.
Individual category versus eGFR ≥60 mL/min/1.73 m²: *$P < .05$; **$P < .01$; ***$P < .001$.

to account for nonlinearity in the progression over time. We entered covariates considered to have a potential prognostic impact into the model on an epidemiological basis. They were age, sex, body surface area, history of hypertension, dyslipidemia, diabetes, smoking, coronary artery disease, atrial fibrillation and AVA at inclusion. The association between eGFR and AS progression was assessed by linear regression. Logistic regression analyses were performed to assess the impact of kidney function on rapid progression. Multivariable analyses of mortality and events (aortic valve replacement) were performed using Cox proportional hazards models. The limit of statistical significance was set to $P < .05$. All tests were two-tailed.

RESULTS

Baseline characteristics

Our final cohort consisted of 647 patients (45.5% female), with a mean age of 74.9 ± 11.2 years. The mean eGFR was 64.4 ± 23.3 mL/min/1.73 m². Kidney function was normal or mildly impaired (eGFR ≥60 mL/min/1.73 m²) for 386 (60%) patients, 125 (19%) had CKD stage 3a, 90 (14%) CKD stage 3b, 26 (4%) CKD stage 4 and 20 (3%) kidney failure stage 5, including 16 patients under maintenance dialysis. Baseline characteristics and medications according to the eGFR group are presented in Table 1. Compared with individuals without CKD, patients with a decreased eGFR were more often affected by hypertension ($P < .001$), coronary artery disease ($P = .001$) and/or diabetes ($P < .01$), and had a higher Charlson index ($P < .001$). The baseline and follow-up echocardiographic characteristics are presented in Table 2. Overall, the mean AVA was 1.17 ± 0.29 cm² at baseline and 0.89 ± 0.27 cm² at the last TTE. There were no differences between the CKD groups in terms of baseline aortic valve parameters, AS severity class or ventricular function, except for systolic pulmonary artery pressure ($P < .01$) and the E/E′ ratio ($P = .03$) (Supplementary data, Table S1).

Table 2: Echocardiographic characteristics at baseline and follow-up according to CKD stage.

	eGFR, mL/min/1.73 m^2														
	≥60 (n = 386)			45–59 (n = 125)			30–44 (n = 90)			15–29 (n = 26)			<15 (n = 20)		
Variable	Baseline	Follow-up	P-value	Baseline	Follow-up	P-value	Baseline	Follow-up	P-value	Baseline	Follow-up	P-value	Baseline	Follow-up	P-value
Aortic valve															
Aortic valve area (cm²)	1.18 ± 0.31	0.92 ± 0.28	<.001	1.17 ± 0.30	0.88 ± 0.28	<.001	1.15 ± 0.26	0.85 ± 0.25	<.001	1.11 ± 0.26	0.76 ± 0.21	<.001	1.26 ± 0.25	0.86 ± 0.21	<.001
Indexed aortic valve area (cm²/m²)	0.64 ± 0.17	0.51 ± 0.15	<.001	0.64 ± 0.16	0.49 ± 0.15	<.001	0.62 ± 0.17	0.47 ± 0.16	<.001	0.60 ± 0.13	0.41 ± 0.11	<.001	0.68 ± 0.17	0.48 ± 0.14	<.001
Vmax (m/s)	3.22 ± 0.61	3.85 ± 0.75	<.001	3.20 ± 0.62	3.85 ± 0.71	<.001	3.28 ± 0.62	3.89 ± 0.71	<.001	3.19 ± 0.69	3.97 ± 0.80	<.001	2.95 ± 0.29	3.88 ± 0.68	<.001
Transaortic mean pressure gradient (mmHg)	25.8 ± 11.2	37.3 ± 15.6	<.001	25.5 ± 11.8	37.1 ± 15.4	<.001	26.9 ± 12.2	37.5 ± 14.7	<.001	25.2 ± 12.0	39.0 ± 16.7	<.001	21.0 ± 6.2	38.1 ± 14.6	<.001
Indexed stroke volume (mL/m²)	43.8 ± 10.2	41.8 ± 13.3	.20	43.3 ± 11.4	42.7 ± 13.3	.30	45.2 ± 12.2	40.6 ± 16.2	.85	43.3 ± 7.2	39.4 ± 14.1	.60	50.8 ± 14.1	41.3 ± 10.8	0.55
Left and right ventricular function															
LV end-diastolic diameter (mm)	48.7 ± 5.5	48.2 ± 6.6	.03	48.8 ± 6.3	48.3 ± 6.8	.21	48.5 ± 5.9	48.0 ± 6.3	.55	49.4 ± 4.3	48.7 ± 4.8	.26	48.7 ± 5.0	48.5 ± 6.6	.53
LV end-systolic diameter (mm)	29.9 ± 5.0	29.9 ± 6.0	.36	29.6 ± 5.8	30.2 ± 7.0	.77	29.6 ± 5.5	29.4 ± 6.4	.69	30.4 ± 4.0	31.3 ± 4.5	.10	30.7 ± 6.1	31.6 ± 465	.78
Indexed LV mass (g/m²)	108.3 ± 32.7	114.7 ± 40.9	<.01	106.5 ± 30.3	115.3 ± 36.3	.08	111.5 ± 31.5	118.3 ± 38.7	.01	105.6 ± 31.5	111.6 ± 27.3	.68	116.8 ± 23.8	108.2 ± 30.4	.18
LVEF (%)	65.7 ± 7.5	65.5 ± 8.1	.83	67.1 ± 7.9	65.7 ± 91	.15	66.7 ± 8.8	66.5 ± 10.2	.68	66.0 ± 8.3	64.6 ± 7.3	.46	65.5 ± 10.4	63.2 ± 5.9	.46
Cardiac output (L/min)	6.05 ± 1.4	5.88 ± 1.6	.36	5.73 ± 1.2	5.45 ± 1.4	.02	6.18 ± 1.3	5.74 ± 1.7	.76	6.02 ± 0.9	5.39 ± 1.4	.29	5.46 ± 1.4	5.95 ± 1.2	.23
sPAP (mmHg)	33.1 ± 9.7	36.7 ± 12.2	<.001	34.3 ± 10.2	39.1 ± 14.1	<.001	38.1 ± 13.9	42.9 ± 14.2	.01	38.6 ± 12.3	45.4 ± 13.0	.10	37.9 ± 13.4	43.5 ± 14.5	.48
E/E′ ratio	11.3 ± 4.7	11.8 ± 6.9	.26	11.4 ± 4.5	12.6 ± 6.6	.10	13.4 ± 6.7	14.8 ± 6.8	.17	14.2 ± 4.6	12.6 ± 2.7	.25	10.0 ± 3.6	15.8 ± 7.1	.25

Continuous variables are expressed as the mean ± 1 SD.
LV: left ventricular; sPAP: systolic pulmonary artery pressure.

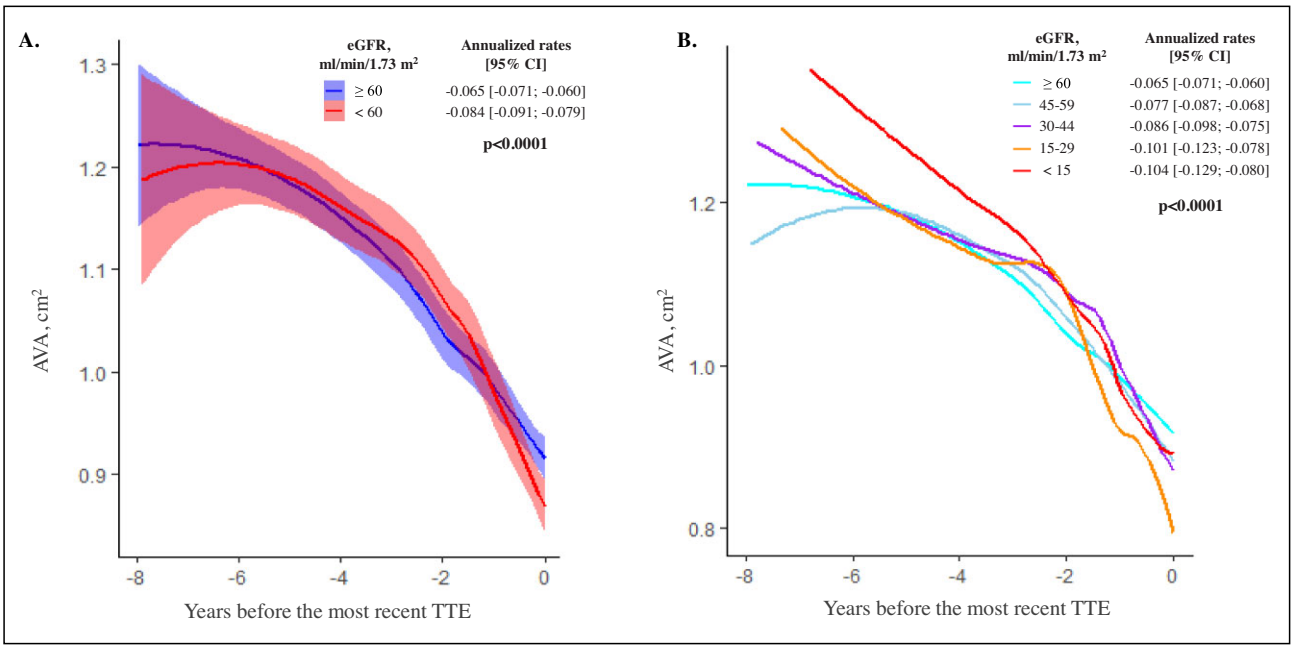


Figure 1: Progression rates of aortic stenosis according to CKD stage. (**A**) Comparison of AS progression rate between patients with CKD (eGFR <60 mL/min/1.73 m^2) and without CKD (eGFR ≥ 60 mL/min/1.73 m^2). (**B**) AS progression rate showed for each CKD stage. The time of the most recent echocardiographic study is considered as time 0. The annualized progression rate of AVA was expressed as mean and 95% CI. The solid line is the overall progression fitted by the adjusted linear mixed-effects model. The shadowed area represents the 95% CI. Analysis were adjusted on age, sex, body surface area, hypertension, dyslipidemia, smoking history, diabetes, coronary artery disease, atrial fibrillation and AVA at baseline.

Progression of aortic stenosis

The mean time between two echocardiographic examinations was 3.6 ± 2.35 years [median 2.9 (IQR 1.8–4.8) years] and 424 patients (65.5%) had three or more TTEs. Overall, the mean progression rate of AVA was –0.077 [95% confidence interval (CI) –0.082; –0.073] cm^2/year. Progression rates were not linear (quadratic time effect: $P < .001$) for the entire cohort. In the linear mixed-effect model adjusted for age, sex, body surface area, history of hypertension, dyslipidemia, diabetes, smoking, coronary artery disease, atrial fibrillation and baseline AVA, patients with normal kidney function had significantly slower mean AVA narrowing [–0.065 (95% CI –0.071; –0.060) cm^2/year] (Fig. 1A) than patients with CKD [–0.084 (95% CI –0.091; –0.078) cm^2/year, $P < .001$]. There was an inverse relationship between the progression rate and kidney function. The more severe the CKD stage, the greater the AVA narrowing (Fig. 1B). The most rapid progression was observed for kidney failure patients [–0.104 (95% CI –0.129; –0.080) cm^2/year, $P < .001$]. The indexed AVA also showed a significant decrease for each CKD stage. Factors associated with annualized AVA narrowing are shown in Supplementary data, Table S2. In multivariable linear regression analysis adjusted for baseline AS severity and baseline characteristics associated with decreased AVA in univariate analysis, lower eGFR remained independently associated with AS progression ($P < .001$). We also analyzed the association between hemodynamic progression based on Vmax and mean gradient of AS and CKD. In multivariable linear regression analysis, we observed that lower eGFR was independently associated with annualized increased in Vmax ($P < .001$) and mean gradient ($P < .001$). Comparable results were found when we used the MDRD equation or the 2021 CKD-EPI equation to estimate GFR ($P < .001$). CKD patients revealed a greater occurrence of AS severity class progression compared with the control group [hazard ratio (HR) 1.53 (1.20; 1.95), $P = .001$]. We also analyzed data on kidney function at the last TTE. The follow-up serum creatinine value was available for 604 (93.4%) patients. Lower follow-up eGFR remained independently associated with annualized AS progression ($P < .001$). After the exclusion of 16 patients under maintenance dialysis, the mean annual loss in eGFR was 1.48 ± 4.35 mL/min/1.73 m^2 per year. In multivariable linear regression analysis, no significant interaction was found between annualized AS progression and the annualized change in eGFR ($P = .12$) in the study population. However, in patients with an eGFR <45 mL/min/1.73 m^2, the rate of kidney function decline was associated with AS progression ($P = .02$).

Determinants of rapid progression

Rapid progression was defined as progression of AVA above the median value of that observed in the study population [–0.070 (IQR –0.04; –0.14) cm^2/year]. As expected, the time from baseline to the last available TTE was longer for patients with nonrapid progression ($P < .001$). Patients with rapid progression were older, had more comorbid conditions and worse kidney function (Supplementary data, Table S3), but milder baseline AS severity than patients with nonrapid progression (Supplementary data, Table S4). Factors associated with rapid progression are presented in Supplementary data, Table S5. After adjustment, there was an inverse relationship between the risk of rapid progression and both kidney function ($P = .001$) and the initial severity of AVA narrowing ($P < .001$). Other multivariable determinants of rapid progression were age, smoking history and associated coronary artery disease. Lower eGFR was also associated ($P = .045$) with rapid Vmax progression (defined as the annualized progression of Vmax above the median value for patients in this cohort) and rapid mean gradient progression (defined as the annualized progression of mean gradient above the median value for patients in this cohort)

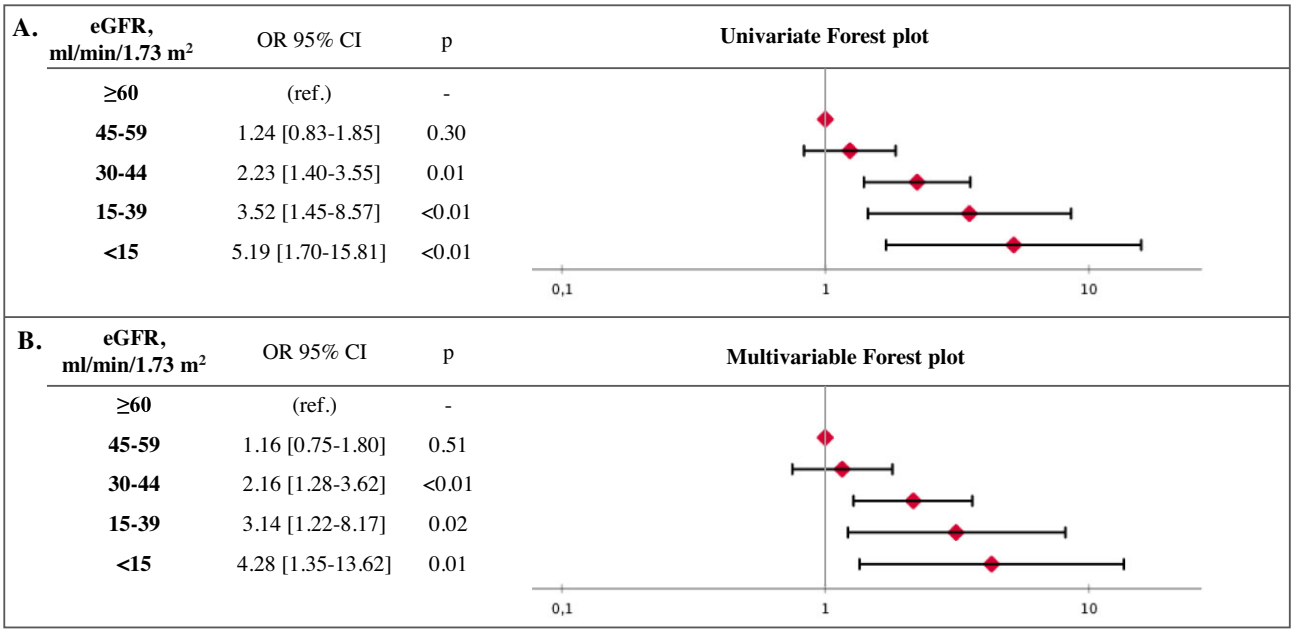


Figure 2: Forest plot showing ORs for association of CKD stage with rapid progression of aortic stenosis. Rapid progression was defined as an annualized decrease in AVA >0.07 cm^2/year. Patients with an eGFR ≥60 mL/min/1.73 m^2 were used as the reference. (**A**) Unadjusted impact of CKD stage on rapid progression of AS. (**B**) Multivariable adjusted effect of CKD stage on rapid progression of AS. Multivariable analysis were adjusted on age, sex, body surface area, hypertension, dyslipidemia, smoking history, diabetes, coronary artery disease, atrial fibrillation and AVA at baseline. Error bars represent the 95% CI.

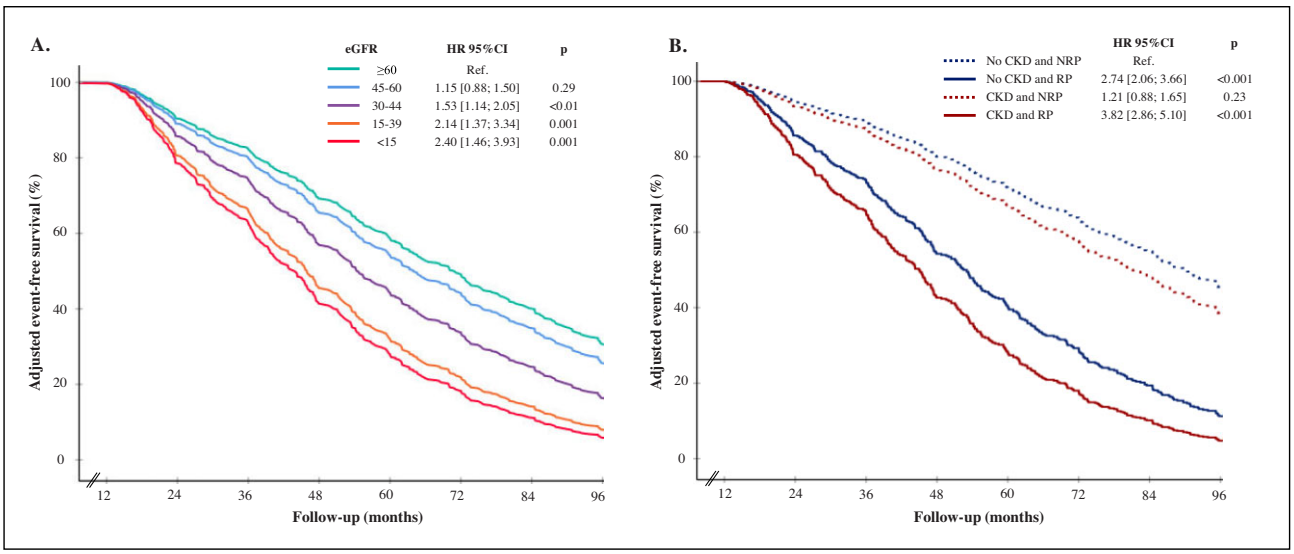


Figure 3: Adjusted event-free (death or aortic valve replacement) survival. (**A**) Impact of kidney function. Patients with an eGFR ≥60 mL/min/1.73 m^2 were used as the reference. (**B**) Impact of kidney function and rapid progression. Patients with an eGFR ≥60 mL/min/1.73 m^2 and nonrapid progression were used as the reference. Multivariable analyses were adjusted for age, sex, body area, hypertension, dyslipidemia, smoking history, diabetes, coronary artery disease, atrial fibrillation and AVA at baseline. All included patients had at least two TTEs, 1 year apart, without any events between these two examinations. RP: rapid progression; NRP: nonrapid progression.

($P = .047$). Moderate CKD was significantly predictive of rapid progression (Fig. 2A). Compared with an eGFR ≥60 mL/min/1.73 m^2, adjusted odds ratios (ORs) for rapid progression increased among patients with CKD stage 3b [adjusted OR 2.16 (95% CI 1.28; 3.62), $P < .01$], CKD stage 4 [adjusted OR 3.14 (95% CI 1.22; 8.17), $P = .02$], and CKD stage 5 [adjusted OR 4.28 (95% CI 1.35; 13.62), $P = .01$] (Fig. 2B). The fully adjusted model showed no association between rapid progression and mild CKD.

Impact of AS progression on aortic valve replacement and survival

During a mean clinical follow up of 3.58 ± 2.35 years, 261 (40.3%) patients died and 219 (33.8%) underwent aortic valve replacement (AVR) (Supplementary data, Table S6). Patients with an eGFR <45 mL/min/1.73 m^2 had a higher adjusted risk of death or having an AVR than patients with normal kidney function (all stages $P < .01$) (Fig. 3A), whereas patients with mild kidney

impairment (eGFR 45–60 mL/min/1.73 m^2) had a similar risk of death or having an AVR as patients with normal kidney function ($P = .29$). After adjustment, patients with CKD and nonrapid progression of AS showed similar event-free survival ($P = .23$) as patients with normal kidney function and nonrapid progression (Fig. 3B). Among patients with rapid progression only, CKD was associated with worse outcomes [HR 2.52 (2.00; 3.18), $P < .001$] (Fig. 3B). Faster progression of AS was an important determinant of the risk of death or having an AVR for both patients without CKD [HR 2.74 (2.06; 3.66), $P < .001$] and patients with CKD [HR 3.29 (2.34; 4.63), $P < .001$]. The risk of all-cause and cardiovascular mortality was considerably higher for patients with an eGFR <45 mL/min/1.73 m^2 (all $P < .01$).

DISCUSSION

The present study documents a significant impact of kidney dysfunction on the rate of AS progression over time: AS progression was more rapid for patients with CKD and increased with decreasing eGFR, even after adjustment for potential confounders. Furthermore, such rapid progression of AS for patients with CKD was associated with worse outcomes. To the best of our knowledge, this association has not been previously documented.

In our cohort, including elderly patients with severe AS, the mean progression rate of AVA was –0.077 (95% CI –0.082; –0.073) cm^2/year after a median follow up of 2.9 years. Our data are consistent with those of previous cohorts. The progression rate described by Yang *et al.* [23] . in a large cohort of AS patients with a Vmax ≥2.5 m/s and preserved LVEF included between 2000 and 2013 with at least two TTEs performed 2 years apart. In a recent study that included 916 patients with mild to severe AS, the annual reduction in AVA was also similar, evaluated to be 0.07 ± 0.003 cm^2/year [24].

CKD is expanding at a worrying rate worldwide [25], and the cardiovascular consequences are such that the risk of death from cardiovascular causes is 10 times greater than that of progressing to dialysis [26]. Although CKD is a common condition for patients with AS and it is known that the prevalence of AS increases as eGFR decreases [1], few studies have been conducted to establish the impact of kidney dysfunction on AS progression. In a study that included 170 patients with severe AS, an association between the rate of reduction in AVA and increase in serum creatinine levels was suggested but did not reach statistical significance ($r = 0.15$, $P = .08$) [10]. The presence of a higher creatinine level for patients with rapid progression than that for patients with nonrapid progression had already been suggested in non-dedicated studies conducted on 78 [27] and 58 patients [28]. However, in multivariate regression analyses, both studies failed to demonstrate a significant relationship between CKD and AS progression, probably related to the small number of CKD patients and to the inappropriate definition of kidney dysfunction as an increase in serum creatinine levels above a threshold. In the present study, CKD was adequately defined according to current KDIGO recommendations based on the eGFR. In the absence of repeated albuminuria measurements in current practice, no information was available regarding patients' albuminuria category (A1–A3) in our study. Our control group (eGFR ≥60 mL/min/1.73 m^2) was based only on kidney function. Albuminuria is a well-known risk factor for cardiovascular disease and mortality. Its relationship with the progression of AS was already suggested [29] and needs further investigations.

According to prior studies [8, 9], AS progressed faster in patients requiring dialysis. Echocardiographic examination of dialysis patients is challenging, as hemodynamic evaluation parameters of the aortic valve may be modified by dialysis session. In our study, TTEs were systematically performed the day after the dialysis session, i.e. 18–24 h after the end of dialysis, which allowed for good "reproducibility" of the measurements. In addition, the presence of a high-flow arteriovenous fistula may be responsible for an increase in trans-valvular flow in association with cardiac high-flow [30]. For these reasons, we also excluded patients who started dialysis during the follow-up.

The link between kidney dysfunction and rapid progression of AS is still unclear. CKD–mineral and bone disorder (i.e. high circulating phosphorus, hyperparathyroidism, increased fibroblast growth factor-23), inflammation and hemodynamic disturbances contribute to the pathophysiology and progression of aortic valve calcification [31]. *In vitro*, an increase in phosphate concentrations is responsible for the differentiation of valvular interstitial cells toward an osteoblastic phenotype [32]. Systemic chronic low-grade inflammation, highly prevalent in patients with chronic dialysis, may also have detrimental effects in the calcification process [33]. The retention of uremic toxins, such as indoxyl-sulfate, appears to have major deleterious cardiovascular effects, including the enhancement of calcification [34]. Fluid overload exacerbates shear stress and may play a role in the calcification process in dialysis patients [35]. However, the impact of each mechanism and their synergy are yet to be defined, especially for patients with mild to moderate kidney dysfunction, and should thus be assessed in further studies.

Vitamin K antagonists (VKAs), commonly used to reduce thromboembolic risk in atrial fibrillation, have been incriminated as a putative cause of accelerated cardiovascular calcification in patients on hemodialysis. Interestingly, warfarin use has recently been associated with aortic stenosis progression [36]. In our study, 109 of 647 patients (16.8%) were treated with VKAs and the proportion of VKAs users was higher among patients with lower eGFR (Table 1). However, univariate linear regression did not show any association between VKAs use and AVA change ($P = .36$) (Supplementary data, Table S2) and non-significant findings were obtained by the logistic regression [OR 0.99 (0.66–1.49), $P = .96$] (Supplementary data, Table S5); the use of VKAs cannot thus be considered as a confounding factor in this study. Confirming this observation, the association between annualized AVA reduction and kidney function decline remained significant even after adjusting for VKAs treatment instead of atrial fibrillation in our multivariate models ($P < .01$ for eGFR or CKD stage, data not shown).

AVR appears to be associated with improved survival of CKD patients relative to conservative management, despite higher perioperative mortality and adverse outcomes [4]. We observed that the risk of death was considerably higher for patients with a combination of CKD and rapid AS progression. This may reflect the risk factors shared between the two conditions. However, adjustment for age, cardiovascular comorbidity, and traditional risk factors did not materially affect our results. The impact of AVR in asymptomatic patients with CKD and rapid progression requires further studies. There is a close relationship between AS progression and kidney function even in non-dialysis patients. Assessment of kidney function should be routinely performed in the follow-up of patients diagnosed with AS. Our observation also suggests that a dedicated expertise of risk factors specific to CKD could improve patients' outcomes. In clinical practice, the evaluation and management of these complex and multifaceted diseases require a collaborative input. Therefore, nephrologist should be an integral component of the heart–kidney team in the management of patients with concomitant AS and CKD. Besides, as evidence-based

medical management of AS in CKD patients is lacking, the efficacy and safety of several therapies that mitigate CKD progression need to be investigated.

Study limitations

Our study had several limitations. First, it was observational and subject to the well-known limitations based on retrospective follow-up data. It thus reflects real-world clinical practice and lacks standardization of the time intervals between consecutive TTE examinations, and does not consider improvements in measurement techniques and equipment upgrades over the years. Second, due to the inclusion of patients with at least two TTEs performed 1 year apart, there was a certain degree of selection bias, and we may not have captured a sufficient number of patients with very rapid progression that required AVR or died during the first year. Third, CT aortic valve scoring was not available in our database. However, specific studies in CKD or dialysis patients are still needed to validate the use of this score in this population. Finally, several disease-specific risk factors (such as CKD–mineral and bone disorders, albuminuria, low-grade inflammation, or the etiology and duration of CKD) may have an influence on AS progression. Unfortunately, since information regarding these factors was not available and given the retrospective nature of our work, the relationship between those parameters and AS progression was impossible to evaluate in our study.

CONCLUSIONS

This study of a large cohort of patients with AS and varying degrees of CKD sheds new light on the impact of kidney dysfunction among non-dialysis patients on AS progression. The progression rate increases with lower eGFR, suggesting a "dose–response" association, even for patients with moderate CKD. Patients with kidney dysfunction should be closely monitored and those with rapid progression seriously considered for AVR decision making. The investigation of potential mechanisms underlying faster progression in CKD patients and the evaluation of mitigation strategies are also urgently needed.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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AUTHORS' CONTRIBUTIONS

All authors contributed to data collection, study design, data analysis, interpretation, and drafting of this paper.

CONFLICT OF INTEREST STATEMENT

None declared by the authors. The results of this paper have not been published elsewhere except in Abstract format at WCN'23.

DATA AVAILABILITY STATEMENT

The database cannot be disclosed to any third party without the prior written consent of all data providers, but the database will be made available to the editorial offices of medical journals when requested. Research proposals can be submitted to our group at tribouilloy.christophe@chu-amiens.fr.

REFERENCES

1. Vavilis G, Bäck M, Occhino G *et al.* Kidney dysfunction and the risk of developing aortic stenosis. *J Am Coll Cardiol* 2019;**73**:305–14. https://doi.org/10.1016/j.jacc.2018.10.068.
2. Coresh J, Selvin E, Stevens LA *et al.* Prevalence of chronic kidney disease in the United States. *JAMA* 2007;**298**:2038–47. https://doi.org/10.1001/jama.298.17.2038.
3. Brück K, Stel VS, Gambaro G *et al.* CKD prevalence varies across the European general population. *J Am Soc Nephrol* 2016;**27**:2135–47. https://doi.org/10.1681/ASN.2015050542.
4. Bohbot Y, Candellier A, Diouf M *et al.* Severe aortic stenosis and chronic kidney disease: outcomes and impact of aortic valve replacement. *J Am Heart Assoc* 2020;**9**:e017190. https://doi.org/10.1161/JAHA.120.017190.
5. Patel KK, Shah SY, Arrigain S *et al.* Characteristics and outcomes of patients with aortic stenosis and chronic kidney disease. *J Am Heart Assoc* 2019;**8**:e009980. https://doi.org/10.1161/JAHA.118.009980.
6. Samad Z, Sivak JA, Phelan M *et al.* Prevalence and outcomes of left-sided valvular heart disease associated with chronic kidney disease. *J Am Heart Assoc* 2017;**6**:e006044. https://doi.org/10.1161/JAHA.117.006044.
7. Ureña-Torres P, D'Marco L, Raggi P *et al.* Valvular heart disease and calcification in CKD: more common than appreciated. *Nephrol Dial Transplant* 2019;**35**:2046–53. https://doi.org/10.1093/ndt/gfz133.
8. Perkovic V, Hunt D, Griffin SV *et al.* Accelerated progression of calcific aortic stenosis in dialysis patients. *Nephron Clin Pract* 2004;**94**:c40–5. https://doi.org/10.1159/000071280.
9. Kim D, Shim CY, Hong GR *et al.* Effect of end-stage renal disease on rate of progression of aortic stenosis. *Am J Cardiol* 2016;**117**:1972–7. https://doi.org/10.1016/j.amjcard.2016.03.048.
10. Palta S, Pai AM, Gill KS *et al.* New insights into the progression of aortic stenosis: implications for secondary prevention. *Circulation* 2000;**101**:2497–502. https://doi.org/10.1161/01.CIR.101.21.2497.
11. Stewart BF, Siscovick D, Lind BK *et al.* Clinical factors associated with calcific aortic valve disease. *J Am Coll Cardiol* 1997;**29**:630–4. https://doi.org/10.1016/S0735-1097(96)00563-3.
12. Koos R, Brandenburg V, Mahnken AH *et al.* Association of fetuin-A levels with the progression of aortic valve calcification in non-dialyzed patients. *Eur Heart J* 2009;**30**:2054–61. https://doi.org/10.1093/eurheartj/ehp158.
13. Marwick TH, Amann K, Bangalore S *et al.* Chronic kidney disease and valvular heart disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int* 2019;**96**:836–49. https://doi.org/10.1016/j.kint.2019.06.025.
14. Charlson ME, Pompei P, Ales KL *et al.* A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987;**40**:373–83. https://doi.org/10.1016/0021-9681(87)90171-8.
15. Nashef SA, Roques F, Sharples LD *et al.* EuroSCORE II. *Eur J Cardiothorac Surg* 2012;**41**:734–44. https://doi.org/10.1093/ejcts/ezs043.
16. Baumgartner H, Hung J, Bermejo J *et al.* Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography.

Eur Heart J Cardiovasc Imaging 2017;**18**:254–75. https://doi.org/10.1093/ehjci/jew335.
17. Lang RM, Badano LP, Mor-Avi V *et al.* Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr* 2015;**28**:1–39.e14. https://doi.org/10.1016/j.echo.2014.10.003.
18. Baumgartner H, Hung J, Bermejo J *et al.* Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr* 2017;**30**:372–92. https://doi.org/10.1016/j.echo.2017.02.009.
19. Levey AS, Stevens LA, Schmid CH *et al.* A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604–12. https://doi.org/10.7326/0003-4819-150-9-200905050-00006.
20. Levey AS, de Jong PE, Coresh J *et al.* The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int* 2011;**80**:17–28. https://doi.org/10.1038/ki.2010.483.
21. Levey AS. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. *Ann Intern Med* 1999;**130**:461. https://doi.org/10.7326/0003-4819-130-6-199903160-00002.
22. Inker LA, Eneanya ND, Coresh J *et al.* New creatinine- and cystatin c-based equations to estimate GFR without race. *N Engl J Med* 2021;**385**:1737–49. https://doi.org/10.1056/NEJMoa2102953.
23. Yang LT, Boler A, Medina-Inojosa JR *et al.* Aortic stenosis progression, cardiac damage, and survival. *JACC Cardiovasc Imaging* 2021;**14**:1113–26. https://doi.org/10.1016/j.jcmg.2021.01.017.
24. Kebed K, Sun D, Addetia K *et al.* Progression of aortic stenosis and echocardiographic criteria for its severity. *Eur Heart J Cardiovasc Imaging* 2020;**21**:737–43. https://doi.org/10.1093/ehjci/jeaa075.
25. Kovesdy CP. Epidemiology of chronic kidney disease: an update 2022. *Kidney Int Suppl* 2022;**12**:7–11. https://doi.org/10.1016/j.kisu.2021.11.003.
26. Weiner DE. Chronic kidney disease as a risk factor for cardiovascular disease and all-cause mortality: a pooled analysis of community-based studies. *J Am Soc Nephrol* 2004;**15**:1307–15. https://doi.org/10.1097/01.ASN.0000123691.46138.E2.
27. Bahler RC, Desser DR, Finkelhor RS *et al.* Factors leading to progression of valvular aortic stenosis. *Am J Cardiol* 1999;**84**:1044–8. https://doi.org/10.1016/S0002-9149(99)00496-8.
28. Wongpraparut N, Apiyasawat S, Crespo G *et al.* Determinants of progression of aortic stenosis in patients aged ≥40 years. *Am J Cardiol* 2002;**89**:350–2. https://doi.org/10.1016/S0002-9149(01)02241-X.
29. Choi YJ, Park JB, Hwang IC *et al.* Proteinuria is an independent predictor of rapid progression of mild to moderate aortic stenosis in patients with preserved renal function. *Int J Cardiovasc Imaging* 2019;**35**:481–9. https://doi.org/10.1007/s10554-018-1473-3.
30. Ennezat PV, Maréchaux S, Pibarot P. From excessive high-flow, high-gradient to paradoxical low-flow, low-gradient aortic valve stenosis: hemodialysis arteriovenous fistula model. *Cardiology* 2010;**116**:70–2. https://doi.org/10.1159/000314938.
31. Lindman BR, Clavel MA, Mathieu P *et al.* Calcific aortic stenosis. *Nat Rev Dis Primer* 2016;16006. https://doi.org/10.1038/nrdp.2016.6.
32. Lu C, Dong X, Yu WP *et al.* Inorganic phosphate-osteogenic induction medium promotes osteogenic differentiation of valvular interstitial cells via the BMP-2/Smad1/5/9 and RhoA/ROCK-1 signaling pathways. *Am J Transl Res* 2020;**12**:3329–45.
33. Hénaut L, Candellier A, Boudot C *et al.* New insights into the roles of monocytes/macrophages in cardiovascular calcification associated with chronic kidney disease. *Toxins* 2019;**11**:529. https://doi.org/10.3390/toxins11090529.
34. Gao H, Liu S. Role of uremic toxin indoxyl sulfate in the progression of cardiovascular disease. *Life Sci* 2017;**185**:23–9. https://doi.org/10.1016/j.lfs.2017.07.027.
35. Candellier A, Hénaut L, Morelle J *et al.* Aortic stenosis in patients with kidney failure: is there an advantage for a PD-first policy ? *Perit Dial Int* 2021;**41**:158–67. https://doi.org/10.1177/0896860820941371.
36. Hariri EH, Kassis N, Badwan OZ *et al.* Impact of oral anticoagulation on progression and long-term outcomes of mild or moderate aortic stenosis. *J Am Coll Cardiol* 2022;**80**:181–3. https://doi.org/10.1016/j.jacc.2022.05.011.

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