Universiteit
Leiden
The Netherlands

Aortic valve disease: multimodality imaging for risk stratification and evaluation of therapy

Vollema, E.M.

Citation

Vollema, E. M. (2022, September 6). *Aortic valve disease: multimodality imaging for risk stratification and evaluation of therapy*. Retrieved from https://hdl.handle.net/1887/3455179

Version:	Publisher's Version
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
Downloaded from:	https://hdl.handle.net/1887/3455179

Note: To cite this publication please use the final published version (if applicable).

5

PROGNOSTIC IMPLICATIONS OF RENAL DYSFUNCTION IN PATIENTS WITH AORTIC STENOSIS

E. Mara Vollema, Edgard A. Prihadi, Arnold C.T. Ng,
Tea Gegeneva, Nina Ajmone Marsan, Jeroen J. Bax, Victoria Delgado

Published in Am J Cardiol. 2020;125(7):1108-1114.

ABSTRACT

AORTIC stenosis (AS) and renal dysfunction share risk factors and often occur simultaneously. The influence of renal dysfunction on the prognosis of patients with various grades of AS has not been extensively described.

The present study aimed to assess the prognostic implications of renal dysfunction in a large cohort of patients with aortic sclerosis and AS grades ranging from mild to severe AS. Patients diagnosed with various grades of AS by transthoracic echocardiography were assessed and divided according to renal function by estimated glomerular filtration rate (eGFR). The occurrence of all-cause mortality (primary endpoint) and aortic valve replacement (AVR) was noted.

Of 1178 patients (mean age 70±13 years, 60% male), 327 (28%) had aortic sclerosis, 86 (7%) had mild AS, 285 (24%) had moderate AS and 480 (41%) had severe AS. Renal dysfunction (eGFR <60 ml/min/1.73 m^2) was present in 440 (37%) patients, and moderate to severe AS was observed more often in these patients compared to patients without (70 vs. 62%, respectively; P=0.008). After a median follow-up of 95 [31-149] months, 626 (53%) patients underwent AVR and 549 (47%) patients died. Severely impaired renal function (eGFR <30 ml/min/1.73 m^2) and AVR were independently associated with all-cause mortality after correcting for AS severity.

In conclusion, renal dysfunction is highly prevalent in patients with various grades of AS. After correcting for AS severity and AVR, severely impaired renal function (eGFR <30 ml/min/1.73 m^2) was independently associated with all-cause mortality. Independent of renal function, AVR was associated with improved survival.

Introduction

Aortic stenosis (AS) and renal dysfunction share several risk factors (e.g., hypertension and diabetes) and often occur simultaneously and with a complex interaction [1]. In patients with end-stage kidney disease, aortic valve calcification has been observed in 28 to 55% of patients, occurs 10 to 20 years earlier and has a faster progression as compared to the general population [1, 2]. Similarly, in patients with milder grades of renal dysfunction, an association between stage of renal dysfunction and grade of aortic valve calcification has been demonstrated and has prognostic implications [3, 4]: moderate and severe AS are present more often in these patients [5, 6] and this has been associated with significantly lower survival as compared to patients with normal renal function [5] or to patients with renal dysfunction without AS [6]. Inversely, renal dysfunction is a frequent finding in severe AS patients undergoing either surgical or transcatheter aortic valve replacement (AVR) and has been associated with poor short- and mid-term outcomes after intervention [7–12]. The influence of renal dysfunction on the prognosis of patients with various grades of AS has not been extensively described. The present study aimed to assess the prognostic implications of renal dysfunction in a large cohort of patients with aortic sclerosis and patients with various grades of AS.

Methods

From an ongoing registry at the Leiden University Medical Center (Leiden, the Netherlands), 1178 patients diagnosed with various grades of AS between May 1994 and June 2017 were included in this retrospective study. Patients were selected based on available baseline echocardiographic data for assessment of AS severity (defined as the first available echocardiographic study performed) and renal function measurement. As currently recommended by international guidelines, the grade of AS severity was determined based on mean aortic valve gradient, peak aortic jet velocity and calculated aortic valve area [13]. Patients were divided according to the following AS severity categories: aortic sclerosis, mild AS, moderate AS and severe AS [13]. Clinical history, physical examination and transthoracic echocardiography were performed at the time of first AS diagnosis for each patient. Clinical data were collected by review of the patient files at the departmental cardiology information system (EPD-vision; Leiden University Medical Center, Leiden, the Netherlands) and hospital electronic medical records (HiX; ChipSoft, Amsterdam, the Netherlands). Baseline clinical data included patient demographics, cardiovascular risk factors, use of cardiovascular medication and laboratory results such as hemoglobin and creatinine level. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used to calculate the estimated glomerular filtration rate (eGFR) [14]. Patients were divided into four groups according to the eGFR as recommended by the current guidelines: normal renal function (eGFR ≥90 ml/min/1.73 m^2), mildly impaired renal function (eGFR 60-89 ml/min/1.73 m^2), moderately impaired renal function (eGFR 30-59 ml/min/1.73 m^2) and severely impaired renal function (eGFR <30 ml/min/1.73 m^2) [15]. Exclusion criteria included subvalvular or supravalvular AS, dynamic subaortic obstruction, active endocarditis and previous AVR. For this retrospective analysis of clinically acquired data, the institutional review board waived the need for patient written informed consent.

Transthoracic echocardiography was performed using commercially available ultrasound systems (System 5, Vivid 7 or E9, General Electric Vingmed, Horten, Norway) equipped with 3.5MHz or M5S transducers with the patient in the left lateral decubitus position. Images were stored digitally on hard disk and analysed offline (EchoPac version BT13; GE Medical Systems). Measurements of the echocardiographic data were performed de novo by experienced observers. Two-dimensional, colour, continuous and pulsed-wave Doppler data from the parasternal and apical views were acquired. Left ventricular (LV) dimensions were measured on the parasternal long-axis view and the LV mass was calculated and indexed for body surface area [16]. The end-diastolic and end-systolic LV volumes were measured on the apical 2- and 4-chamber views using the Simpson's biplane method and the LV ejection fraction was calculate [16]. Continuous-wave Doppler recordings of the 3- or 5-chamber apical views were obtained for estimation of the peak aortic jet velocity [13]. Using the simplified Bernoulli equation, the peak and mean gradients of the aortic valve were calculated [13]. On the 3- or 5-chamber apical views, pulsed-wave Doppler recordings of the flow through the LV outflow tract were obtained to derive the velocity-time integral and the aortic valve area (AVA) was calculated according to the continuity equation [13]. AS severity was classified according to the current recommendations: aortic sclerosis was defined as calcification and thickening of the aortic valve with a peak aortic jet velocity ≤2.5 m/s; mild AS was defined as a peak aortic jet velocity of 2.6-2.9 m/s, a mean gradient <20 mmHg or an AVA >1.5 cm^2; moderate AS was defined as a peak aortic jet velocity of 3.0-4.0 m/s, a mean gradient of 20-40 mmHg or an AVA of 1.0-1.5 cm^2; and severe AS was defined as a peak aortic jet velocity ≥4.0 m/s, a mean gradient ≥40 mmHg or an AVA <1.0 cm^2 [13].

Occurrence of surgical or transcatheter AVR and all-cause death from the moment of the first diagnosis of AS at baseline echocardiography to the last follow-up was noted for all patients. The primary endpoint of all-cause mortality was assessed through individual patient record review, linked to the governmental death registry database.

Continuous variables are presented as mean±standard deviation when normally distributed and compared across patient groups divided according to the renal function category using the analysis of variance (ANOVA) test. When not normally distributed, continuous variables were presented as median and interquartile range (IQR) and compared across groups using the Kruskal-Wallis test. Categorical variables were presented as numbers and percentages and compared using χ^2 tests. Cumulative event-free survival from all-cause mortality was calculated using the Kaplan Meier method and log-rank tests were performed for comparison across groups. For the identification of clinical and echocardiographic parameters associated with all-cause mortality, univariable Cox proportional hazard regression analyses were performed. Significant univariable variables (P <0.05) were then introduced as covariates in a multivariable Cox proportional hazards regression model to identify demographic, clinical and echocardiographic variables independently associated with all-cause mortality. The occurrence of surgical or transcatheter AVR was entered as a time-dependent covariate and was forced into the multivariable model. Hazard ratios (HRs) with 95% confidence intervals (CI) were presented. The validity of the assumption of proportional hazards for the Cox regression analyses was confirmed for all categorical variables using log minus log plots. For continuous variables, the proportional hazard assumption was confirmed using partial

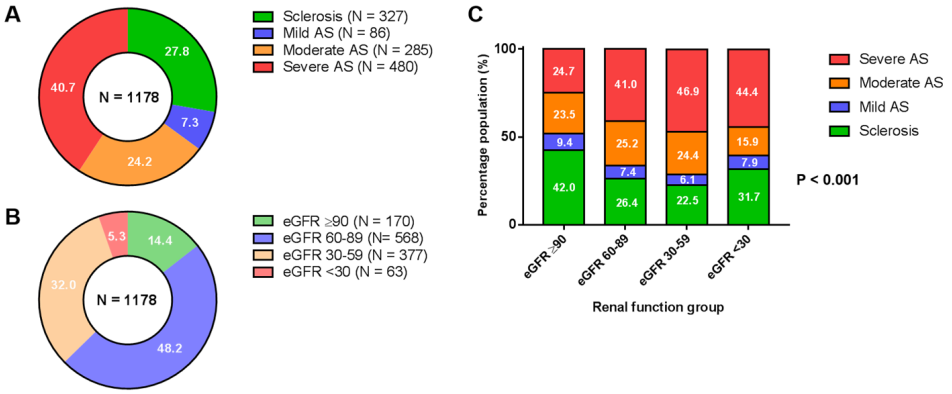

Figure 1: Distribution of grade of aortic stenosis (*panel A*) and renal function (*panel B*) in total study population and of various grades of aortic stenosis across renal function groups (*panel C*). AS, aortic stenosis; eGFR, estimated glomerular filtration rate.

residuals (i.e., Schoenfeld residuals). SPSS software (version 23.0; IBM, Armonk, NY) was used for the statistical analyses. A two-sided P value <0.05 was considered statistically significant.

Results

The total study population consisted of 1178 patients (mean age 70.1±13.0 years, 60% male) diagnosed with aortic sclerosis and various grades of AS: 327 (27.8%) patients had aortic sclerosis, 86 (7.3%) patients had mild AS, 285 (24.2%) patients had moderate AS and 480 (40.7%) patients had severe AS (Figure 1 *panel A*). The population was divided into four groups based on the renal function: normal renal function (eGFR ≥90 ml/min/1.73 m^2) was present in 170 (14.4%) patients, mildly impaired renal function (eGFR 60-89 ml/min/1.73 m^2) in 568 (48.2%) patients, moderately impaired renal function (eGFR 30-59 ml/min/1.73 m^2) in 377 (32.0%) patients and severely impaired renal function (eGFR <30 ml/min/1.73 m^2) in 63 (5.3%) patients (Figure 1 *panel B*). The distribution of the various grades of AS across the renal function groups is depicted in Figure 1 *panel C*: there was a higher prevalence of moderate to severe AS in patients with moderately to severely impaired renal function (eGFR <60 ml/min/1.73 m^2) compared to normal to mildly impaired renal function (eGFR ≥60 ml/min/1.73 m^2) patients (69.8% vs. 62.1%, respectively; P=0.008).

Baseline clinical and echocardiographic characteristics for the total study population and according to renal function groups are listed in Table 1 and Table 2. Compared to patients with normal to mildly impaired renal function, patients with moderately to severely impaired renal function were older, more often had New York Heart Association class ≥III symptoms, more often had cardiovascular risk factors and comorbidities such as diabetes, coronary artery disease, previous myocardial infarction and atrial fibrillation and therefore more often used cardiovascular medication (Table 1). On echo-

Table 1: Baseline clinical characteristics of the total study population and according to renal function group.

Variables	Total population (N = 1178)	eGFR ≥90 ml/min/1.73 m^2 (N = 170)	eGFR 60-89 ml/min/1.73 m^2 (N = 568)	eGFR 30-59 ml/min/1.73 m^2 (N = 377)	eGFR <30 ml/min/1.73 m^2 (N = 63)	*P* value
Male gender	706 (60%)	114 (67%)	334 (59%)	219 (58%)	39 (62%)	0.209
Age (years)	70.1±13.0	55.2±15.3	70.7±10.7	75.7±9.1	70.8±13.9	**<0.001**
Body surface area (m^2)	1.88±0.20	1.90±0.21	1.88±0.20	1.86±0.20	1.87±0.18	0.214
Systolic blood pressure (mmHg)	143±29	140±22	144±26	144±28	143±29	0.323
Diastolic blood pressure (mmHg)	78±14	79±13	78±13	77±14	78±15	0.492
Heart rate (beats per minute)	74±15	73±14	74±15	73±15	76±16	0.613
NYHA class III-IV symptoms	295 (26%)	18 (11%)	138 (25%)	124 (34%)	15 (24%)	**<0.001**
Hypertension	629 (55%)	63 (38%)	293 (53%)	238 (65%)	35 (56%)	**<0.001**
Hypercholesterolemia	376 (34%)	40 (24%)	195 (37%)	126 (36%)	15 (25%)	**0.011**
Diabetes mellitus	232 (20%)	29 (17%)	97 (18%)	92 (25%)	14 (22%)	**0.040**
Previous myocardial infarction	199 (17%)	17 (10%)	93 (17%)	73 (19%)	16 (25%)	**0.015**
Atrial fibrillation	205 (18%)	17 (10%)	97 (18%)	73 (20%)	18 (29%)	**0.005**
COPD	155 (13%)	14 (8%)	77 (14%)	59 (16%)	5 (8%)	0.061
Creatinin level (μmol/L)	89 [74-109]	67 [57-76]	81 [72-93]	115 [100-132]	255 [181-528]	**<0.001**
eGFR CKD-EPI (ml/min/1.73 m^2)	66.6±22.6	100.0±10.7	74.4±8.5	47.6±8.3	18.8±12.3	**<0.001**
Hemoglobin (mmol/L)	8.2±1.2	8.3±1.3	8.4±1.1	8.2±1.1	7.0±1.1	**<0.001**
Urea (mmol/L)	6.9 [5.4-9.0]	5.1 [4.2-6.1]	6.5 [5.4-7.9]	9.1 [7.2-11.5]	19.2 [13.4-25.8]	**<0.001**
Medication use						
Beta blocker	499 (44%)	55 (33%)	234 (43%)	179 (48%)	31 (51%)	**0.006**
ACE inhibitor/ARB	507 (44%)	52 (31%)	236 (43%)	188 (51%)	31 (51%)	**<0.001**
Diuretics	417 (36%)	33 (20%)	171 (31%)	183 (49%)	30 (49%)	**<0.001**
Calcium antagonists	257 (22%)	29 (17%)	111 (20%)	99 (27%)	18 (30%)	**0.023**
Statin	508 (44%)	54 (32%)	250 (46%)	172 (46%)	32 (53%)	**0.006**
Anticoagulation/antiplatelet	598 (52%)	54 (32%)	289 (53%)	220 (59%)	35 (57%)	**<0.001**

Continuous variables are presented as mean±SD or median [25th -75th percentile]. CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; NYHA, New York Heart Association.

Table 2: Echocardiographic parameters of the total study population and according to renal function group.

Variables	Total population (N = 1178)	eGFR ≥90 ml/min/1.73 m^2 (N = 170)	eGFR 60-89 ml/min/1.73 m^2 (N = 568)	eGFR 30-59 ml/min/1.73 m^2 (N = 377)	eGFR <30 ml/min/1.73 m^2 (N = 63)	*P* value
Aortic valve morphology						**<0.001**
Tricuspid	1079 (92%)	132 (78%)	524 (92%)	363 (96%)	60 (95%)	
Bicuspid	99 (8%)	38 (22%)	44 (8%)	14 (4%)	3 (5%)	
Significant aortic regurgitation	10 (1%)	0 (0%)	5 (1%)	4 (1%)	1 (2%)	0.558
Significant mitral regurgitation	42 (4%)	2 (1%)	20 (4%)	19 (5%)	1 (2%)	0.115
LV end-diastolic diameter (mm)	48.5±7.6	48.5±6.4	48.3±7.5	48.7±8.5	49.2±6.4	0.807
Septal wall thickness (mm)	12.2±2.3	11.7±2.3	12.1±2.2	12.5±2.3	12.4±2.2	**0.002**
Posterior wall thickness (mm)	11.8±2.0	11.4±2.0	11.8±2.0	12.0±2.1	12.3±2.5	**0.013**
LV mass index (g/m^2)	121.4±36.6	113.5±35.4	119.7±34.8	126.0±38.2	130.0±39.9	**<0.001**
LV ejection fraction (%)	55.7±12.0	59.4±8.3	55.9±11.9	54.5±13.1	53.1±13.1	**<0.001**
Stroke volume index (ml/m^2)	41.9±12.8	44.8±11.7	42.2±12.9	40.3±12.7	40.8±13.3	**0.002**
Peak aortic jet velocity (m/s)	3.1±1.1	2.8±1.2	3.2±1.1	3.2±1.1	3.0±1.2	**0.001**
Mean aortic valve gradient (mmHg)	27.4±19.3	23.2±19.8	27.7±18.6	29.2±19.6	25.6±20.2	**0.007**
Aortic valve area (cm^2)	1.29±0.65	1.58±0.74	1.27±0.63	1.18±0.58	1.31±0.78	**<0.001**

Continuous variables are presented as mean±SD or median [25th -75th percentile]. eGFR, estimated glomerular filtration rate; LV, left ventricular.

cardiography, patients with moderately to severely impaired renal function had a larger LV mass index, lower LV ejection fraction and higher mean aortic valve gradient than patients with less than moderately impaired renal function (Table 2).

After a median follow-up of 95 [IQR: 31-149] months, 626 (53%) patients underwent AVR (63% had a surgical AVR and 37% a transcatheter AVR) and 549 (47%) patients died. The distribution of all-cause mortality across the renal function groups is shown in Table 3.

Figure 2 *panel A* shows the Kaplan-Meier curves of cumulative event-free survival for the various renal function groups. At 10 years, the cumulative survival rates were significantly lower for patients with moderately and severely impaired renal function compared to patients with mildly impaired and normal renal function (43% and 19% vs. 61% and 76%, respectively, log-rank *P*<0.001). To determine the prognostic effect of AS severity grade, the study population was divided by the presence of moderate to severe AS and renal dysfunction (defined as eGFR <60 ml/min/1.73 m^2)(Figure 2 *panel B*). Amongst patients without renal dysfunction, patients with moderate to severe AS had lower 10-year cumulative event-free survival rates than patients with less than moderate AS (61% vs. 70%, respectively; log-rank *P*=0.015). However, amongst patients with renal dysfunction, no additional effect of AS severity on 10-year cumulative event-free survival rates was observed (39% for less than moderate AS vs. 40% for moderate to severe AS, log-rank *P*=0.636).

For the evaluation of the independent associates of all-cause mortality, a multivariable Cox proportional hazards regression model was constructed (Table 4). To take into account the effect of AVR on survival, AVR was introduced as a time-dependent covariate and forced into the multivariable model. In the univariable analysis, multiple parameters were significantly associated with all-cause mortality: renal function, age, hypertension, diabetes, previous myocardial infarction, atrial fibrillation, LV ejection fraction, LV mass index and AVA. On multivariable analysis, renal function (HR: 0.99; 95% CI 0.98-0.99; *P*<0.001) and surgical or transcatheter AVR (HR: 0.67; 95% CI 0.54-0.85; *P*=0.001) were independently associated with all-cause mortality, together with age, diabetes, previous myocardial infarction and LV ejection fraction (Table 4). When regarded as a categorical variable, only severely impaired renal function was independently associated with all-cause mortality (HR: 3.24; 95% CI 2.02-5.21; *P*<0.001).

Table 3: Outcomes of the total study population and according to renal function group.

Population	**All-cause mortality, *N* (%)**	***P* value**
Total population (N = 1178)	549 (47)	
According to renal function group		**<0.001**
eGFR ≥90 ml/min/1.73 m^2 (N = 170)	45 (27)	
eGFR 60-89 ml/min/1.73 m^2 (N = 568)	242 (43)	
eGFR 30-59 ml/min/1.73 m^2 (N = 377)	211 (56)	
eGFR <30 ml/min/1.73 m^2 (N = 63)	51 (81)	

eGFR, estimated glomerular filtration rate

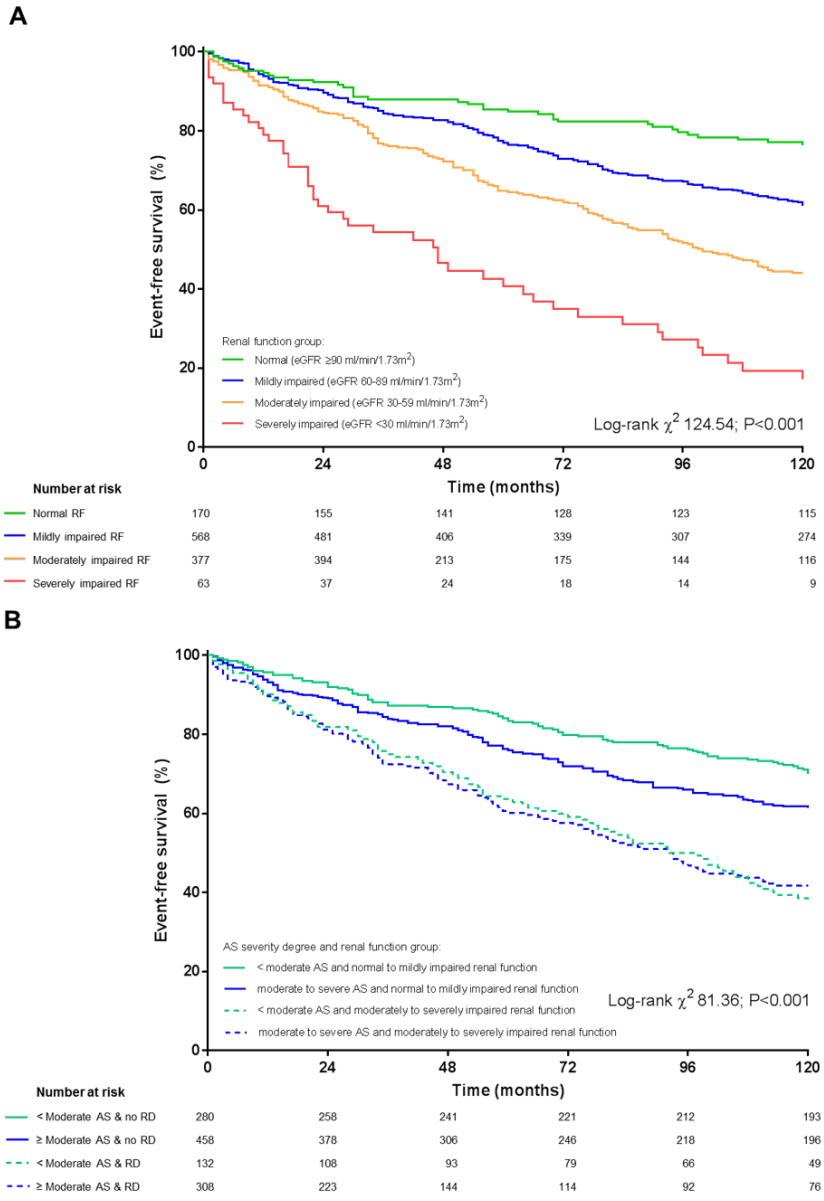

Figure 2: Kaplan-Meier estimates of cumulative event-free survival of study population stratified by (*panel A*) renal function group and (*panel B*) grade of aortic stenosis and presence of renal dysfunction (eGFR <60 ml/min/1.73 m^2). AS, aortic stenosis; eGFR, estimated glomerular filtration rate; RD, renal dysfunction; RF, renal function.

Table 4: Univariable and multivariable Cox regression analyses to identify independent associates of all-cause mortality.

	Univariate analysis		Multivariate analysis	
Variable	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Age (years)	1.05 (1.04-1.06)	**<0.001**	1.05 (1.04-1.06)	**<0.001**
Male gender	1.10 (0.93-1.31)	0.261		
NYHA class III-IV symptoms	1.15 (0.95-1.41)	0.159		
Hypertension	1.21 (1.02-1.43)	**0.031**	0.98 (0.81-1.19)	0.854
Hypercholesterolemia	0.84 (0.69-1.02)	0.072		
Diabetes mellitus	1.56 (1.29-1.90)	**<0.001**	1.50 (1.21-1.86)	**<0.001**
Previous myocardial infarction	1.80 (1.47-2.19)	**<0.001**	1.45 (1.16-1.80)	**0.001**
Atrial fibrillation	1.38 (1.11-1.71)	**0.003**	0.97 (0.76-1.23)	0.796
LV ejection fraction (%)	0.98 (0.97-0.98)	**<0.001**	0.99 (0.98-0.99)	**0.003**
LV mass index (g/m^2)	1.01 (1.00-1.01)	**<0.001**	1.00 (1.00-1.00)	0.230
Peak aortic jet velocity (m/s)	0.99 (0.91-1.07)	0.723		
Mean aortic valve gradient (mmHg)	1.00 (0.99-1.00)	0.566		
Aortic valve area (cm^2)	0.79 (0.69-0.91)	**0.001**	0.85 (0.71-1.03)	0.096
Aortic valve replacement (surgical or transcatheter)	0.89 (0.74-1.06)	0.189	0.67 (0.54-0.85)	**0.001**
Estimated GFR (ml/min/1.73 m^2)	0.98 (0.98-0.98)	**<0.001**	0.99 (0.98-0.99)	**<0.001**
According to renal function group				
Estimated GFR ≥90 ml/min/1.73 m^2	Reference		Reference	
Estimated GFR 60-89 ml/min/1.73 m^2	1.97 (1.44-2.72)	**<0.001**	1.02 (0.70-1.47)	0.933
Estimated GFR 30-59 ml/min/1.73 m^2	3.23 (2.34-4.46)	**<0.001**	1.22 (0.83-1.81)	0.313
Estimated GFR <30 ml/min/1.73 m^2	6.65 (4.43-9.95)	**<0.001**	3.24 (2.02-5.21)	**<0.001**

CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio; LV, left ventricular; NYHA, New York Heart Association.

Discussion

The present study showed that renal dysfunction (eGFR <60 ml/min/1.73 m^2) is highly prevalent in a large cohort of patients with various grades of AS. Even after correcting for AS severity and surgical or transcatheter AVR, severely impaired renal function (eGFR <30 ml/min/1.73 m^2) was independently associated with all-cause mortality. Surgical or transcatheter AVR was associated with improved survival, independent of renal function. This suggests that patients undergoing AVR have a survival benefit, even in the presence of severely impaired renal function.

Renal dysfunction and aortic stenosis share several risk factors (e.g., hypertension, diabetes mellitus, hypercholesterolemia and smoking) and often coexist [1]. However, the bidirectional interaction between renal dysfunction and AS is complex and not completely understood. It is increasingly recognized that an active process very similar to atherosclerosis underlies aortic valve calcification (AVC), the precursory phase of AS [17, 18].

An increased prevalence and more rapid progression of AVC and AS has been observed in end-stage renal disease patients: AVC has been observed in 28 to 55% of these patients with a 10-20 year earlier onset as compared to patients without renal disease [1, 2, 19]. Studies on the prevalence of AVC and AS in patients with less severe renal disease have reported conflicting results: although Guerraty et al. [3] reported an independent and dose-dependent association of eGFR with AVC, the majority of studies did not find a significant association [20–22]. Focussing on AS, renal disease was shown to be associated with a doubling of yearly AS progression rate in moderate AS patients [23]. Vavilis et al. recently demonstrated that in 1,121,875 patients (of which 66,949 [6.0%] patients had renal dysfunction), the risk for development of AS was associated with eGFR in a dose-dependent manner [4]. Furthermore, Samad et al. evaluated 78,059 patients (including 23,727 [30%] patients with eGFR <60 ml/min/1.73 m^2), and described that patients with renal dysfunction had higher odds of having mild and moderate AS compared to patients without (odds ratio [OR] 1.30 (95% CI 1.18-1.43) and OR 1.22 (95% CI 1.07-1.40), respectively; P<0.001) [5]. In patients with renal dysfunction and at least mild AS, the presence of AS was associated with worse survival as compared to renal dysfunction patients without AS (P<0.001) and lower eGFR was associated with an increased risk for all-cause mortality (HR: 1.18 [95% CI 1.08–1.29]) [6]. Inversely, renal dysfunction is commonly reported in severe AS patients undergoing AVR, with prevalence rates of 25 to 34% in surgical AVR [7, 24] and of 38 to 70% in transcatheter AVR patients [8, 10–12, 25]. The prevalence of renal dysfunction in more varying grades of AS has not been well described. The present study corroborates and extends earlier findings by showing that renal dysfunction is prevalent in a population with aortic sclerosis and AS grades ranging from mild to severe AS.

Preoperative renal dysfunction has been demonstrated to negatively influence both short- and long-term survival of severe AS patients undergoing either surgical or transcatheter AVR [7, 9–11, 24]. Importantly, the Euro Heart Survey reported that renal dysfunction was an important reason for denying intervention when indicated [26]. The prognostic value of renal dysfunction has not been extensively evaluated in less than severe AS patients. The present study demonstrates and corroborates earlier findings that severely impaired renal function is significantly associated with all-cause mortality, in-

dependent of AS severity [6]. Furthermore, AVR was shown to have a positive effect on outcome, independent of renal function [6]. This suggests that patients with severely impaired renal function may have survival benefit undergoing AVR, although this needs to be corroborated by future studies.

The present study has limitations inherent to its retrospective design and was performed in a single centre, which is a referral centre for cardiac surgery. This may have introduced selection bias. A considerable part of the study population underwent AVR, which may have a positive impact on prognosis. Although these patients were not equally distributed over the renal function groups, AVR was introduced in the Cox regression analyses as a time-dependent covariate to correct for this potential effect. There can be residual biases due to additional confounders influencing prognosis which have not been taken into account in the analyses (e.g., serum values of calcium and phosphate, systolic pulmonary artery pressure, significant tricuspid regurgitation and right ventricular function) due to lack of systematic recording of these parameters in the database. Classification of patient into renal function groups was based on a single measurement of eGFR, this may have led to misclassification and precluded differentiation between acute and chronic renal dysfunction. Low flow-low gradient severe AS was present in 99 of 480 severe AS patients (20.6%). Data on dobutamine stress echocardiography was unavailable in these patients, and misclassification of AS severity could have occurred. In a small proportion of patients (4%), calculation of AVA was not possible due to missing data on velocity-time integral of the LV outflow tract and AS severity classification was based solely on mean gradient and peak aortic jet velocity [13]. Albuminuria, an important marker for kidney damage [15], was not taken in to account due to lack of systematic determination of these data. For similar reasons, renal replacement therapy and causes of renal dysfunction were not considered in the analyses.

CONCLUSIONS

IN this large single-center study of patients with aortic sclerosis and AS grades ranging from mild to severe AS, renal dysfunction (defined as eGFR <60 ml/min/1.73 m^2) is a prevalent finding. Severely impaired renal function (i.e., eGFR <30 ml/min/1.73 m^2) was independently associated with all-cause mortality (HR: 3.24; 95% CI 2.01-5.20; P<0.001).

REFERENCES

[1] Kahn MR, Robbins MJ, Kim MC, Fuster V. Management of cardiovascular disease in patients with kidney disease. Nat Rev Cardiol. 2013;10(5):261-73.

[2] London GM, Pannier B, Marchais SJ, Guerin AP. Calcification of the aortic valve in the dialyzed patient. J Am Soc Nephrol. 2000;11(4):778-83.

[3] Guerraty MA, Chai B, Hsu JY, Ojo AO, Gao Y, Yang W, et al. Relation of aortic valve calcium to chronic kidney disease (from the Chronic Renal Insufficiency Cohort Study). Am J Cardiol. 2015;115(9):1281-6.

[4] Vavilis G, Bäck M, Occhino G, Trevisan M, Bellocco R, Evans M, et al. Kidney Dysfunction and the Risk of Developing Aortic Stenosis. J Am Coll Cardiol. 2019;73(3):305-14.

[5] Samad Z, Sivak JA, Phelan M, Schulte PJ, Patel U, Velazquez EJ. Prevalence and outcomes of left-sided valvular heart disease associated with chronic kidney disease. J Am Heart Assoc. 2017;6(10):1-15.

[6] Patel KK, Shah SY, Arrigain S, Jolly S, Schold JD, Navaneethan SD, et al. Characteristics and Outcomes of Patients With Aortic Stenosis and Chronic Kidney Disease. J Am Heart Assoc. 2019;8(3):e009980.

[7] Thourani VH, Keeling WB, Sarin EL, Guyton RA, Kilgo PD, Dara AB, et al. Impact of Preoperative Renal Dysfunction on Long-Term Survival for Patients Undergoing Aortic Valve Replacement. Ann Thorac Surg. 2011;91(6):1798-807.

[8] Thourani VH, Forcillo J, Beohar N, Doshi D, Parvataneni R, Ayele GM, et al. Impact of Preoperative Chronic Kidney Disease in 2,531 High-Risk and Inoperable Patients Undergoing Transcatheter Aortic Valve Replacement in the PARTNER Trial. Ann Thorac Surg. 2016;102(4):1172-80.

[9] Gargiulo G, Capodanno D, Sannino A, Perrino C, Capranzano P, Stabile E, et al. Moderate and Severe Preoperative Chronic Kidney Disease Worsen Clinical Outcomes After Transcatheter Aortic Valve Implantation: Meta-Analysis of 4992 Patients. Circulation: Cardiovascular Interventions. 2015;8(2):e002220.

[10] Gupta T, Goel K, Kolte D, Khera S, Villablanca PA, Aronow WS, et al. Association of Chronic Kidney Disease With In-Hospital Outcomes of Transcatheter Aortic Valve Replacement. J Am Coll Cardiol Intv. 2017;10(20):2050-60.

[11] Lüders F, Kaier K, Kaleschke G, Gebauer K, Meyborg M, Malyar NM, et al. Association of CKD with outcomes among patients undergoing transcatheter aortic valve implantation. Clin J Am Soc Nephrol. 2017;12(5):718-26.

[12] Mohananey D, Griffin BP, Svensson LG, Popovic ZB, Tuzcu EM, Rodriguez LL, et al. Comparative Outcomes of Patients With Advanced Renal Dysfunction Undergoing Transcatheter Aortic Valve Replacement in the United States From 2011 to 2014. Circ Cardiovasc Interv. 2017;10(10):e005477.

[13] Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, 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(3):254-75.

[14] Levey AS, Stevens LA, Schmid CH, Zhang Y, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

[15] Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3(1):136-50.

[16] Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, 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. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-71.

[17] Pawade TA, Newby DE, Dweck MR. Calcification in aortic stenosis: the skeleton key. J Am Coll Cardiol. 2015;66(5):561-77.

[18] Linefsky JP, OBrien KD, Katz R, De Boer IH, Barasch E, Jenny NS, et al. Association of serum phosphate levels with aortic valve sclerosis and annular calcification: the cardiovascular health study. J Am Coll Cardiol. 2011;58(3):291-7.

[19] Kim D, Shim CY, Hong GR, Cho IJ, Chang HJ, Ha JW, et al. Effect of End-Stage Renal Disease on Rate of Progression of Aortic Stenosis. Am J Cardiol. 2016;117(12):1972-7.

[20] Ix JH, Shlipak MG, Katz R, Budoff MJ, Shavelle DM, Probstfield JL, et al. Kidney function and aortic valve and mitral annular calcification in the Multi-Ethnic Study of Atherosclerosis (MESA). Am J Kidney Dis. 2007;50(3):412-20.

[21] Fox CS, Larson MG, Vasan RS, Guo CY, Parise H, Levy D, et al. Cross-Sectional Association of Kidney Function with Valvular and Annular Calcification: The Framingham Heart Study. J Am Soc Nephrol. 2006;17(2):521-7.

[22] Hensen LCR, el Mahdiui M, van Rosendael AR, Smit JM, Jukema JW, Bax JJ, et al. Prevalence and Prognostic Implications of Mitral and Aortic Valve Calcium in Patients With Chronic Kidney Disease. Am J Cardiol. 2018;122(10):1732-7.

[23] Ersboll M, Schulte PJ, Al Enezi F, Shaw L, Køber L, Kisslo J, et al. Predictors and progression of aortic stenosis in patients with preserved left ventricular ejection fraction. Am J Cardiol. 2015;115(1):86-92.

[24] Glaser N, Jackson V, Holzmann MJ, Franco-Cereceda A, Sartipy U. Late survival after aortic valve replacement in patients with moderately reduced kidney function. J Am Heart Assoc. 2016;5(12):1-11.

[25] Allende R, Webb JG, Munoz-Garcia AJ, De Jaegere P, Tamburino C, Dager AE, et al. Advanced chronic kidney disease in patients undergoing transcatheter aortic valve implantation: insights on clinical outcomes and prognostic markers from a large cohort of patients. Eur Heart J. 2014;35(38):2685-96.

[26] Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Bärwolf C, Levang OW, et al. A prospective survey of patients with valvular heart disease in Europe: the Euro Heart Survey on valvular heart disease. Eur Heart J. 2003;24(13):1231-43.