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Cardiac mechanics in chronic kidney disease

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CARDIAC MECHANICS IN CHRONIC KIDNEY DISEASE



Liselotte C.R. Hensen

CARDIAC MECHANICS IN CHRONIC KIDNEY DISEASE

LISELOTTE CATHARINA ROSALINA HENSEN

The studies described in this thesis were performed at the Department of Cardiology of the Leiden University Medical Center, Leiden, The Netherlands

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The journey of a thousand miles begins with one single step
Lao Zi (ca. 604-507 v.Chr.)

Voor mijn ouders

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Chapter 1

GENERAL INTRODUCTION AND
OUTLINE OF THE THESIS

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Introduction

Chronic kidney disease (CKD) is a worldwide growing epidemic associated with an increased risk of cardiovascular morbidity and mortality.¹⁻⁴ Heart failure is particularly frequent among patients with CKD.² Pressure and volume overload and non-hemodynamic factors associated with CKD induce left ventricular (LV) hypertrophy, reduce capillary density and increase myocardial fibrosis that lead to LV diastolic and systolic dysfunction.⁵ These processes have been proposed as important determinants of increased mortality in this population.⁵

The most frequent cause of death in patients with advanced CKD is sudden cardiac death; there is an enhanced arrhythmogenicity due to an increased prevalence of cardiac risk factors such as coronary artery disease, LV hypertrophy and myocardial fibrosis, as well as non-cardiac (CKD-specific) risk factors such as electrolyte alterations, sympathetic hyperactivity, uremia and anemia.^{2,6} Patients with CKD also have an increased risk for developing valvular heart disease due to hemodynamic factors and metabolic pathways that promote valvular calcification, cardiac dilatation and infective endocarditis.^{7,8} Finally, atrial fibrillation is particularly frequent in patients with advanced CKD due to electrical and structural remodeling of the atrial myocardium as a consequence of hemodynamic and metabolic disturbances.⁹⁻¹³

Left ventricular systolic dysfunction in patients with chronic kidney disease

LV ejection fraction (LVEF), calculated from two-dimensional echocardiography, is the most frequently used parameter to define LV systolic (dys-)function¹⁴, and is strongly associated with HF and increased mortality in patients with CKD.^{15,16} However, LVEF has been shown rather insensitive to the detection of LV systolic dysfunction, particularly in patients with CKD. In these patients, LV hypertrophy and changes in the LV structure may lead to subtle LV systolic dysfunction despite preserved LVEF.¹⁷ In the last years, several advances in echocardiography resulted in novel indices in order to improve characterization of LV function. Two-dimensional speckle tracking echocardiography provides more insight in cardiac mechanics and LV performance. LV global longitudinal strain (GLS), assessed with two-dimensional speckle tracking echocardiography, may provide more detailed information on LV systolic function.¹⁸ Yet, data on the prevalence of subtle LV systolic dysfunction, according to LV GLS in patients with CKD and preserved

LVEF have not been explored to date. The incremental prognostic value of LV GLS over LVEF has been demonstrated in patients with various cardiovascular diseases (ischemic heart disease, valvular heart disease and heart failure).¹⁹ However, little is known about the association between LV GLS and survival in patients with CKD.¹⁹

LV mechanical dispersion represents LV mechanical dyssynchrony and is measured with two-dimensional speckle tracking echocardiography. LV GLS and LV mechanical dispersion are potential risk markers of ventricular arrhythmias in patients with CKD. Patients with advanced CKD may benefit from an implantable cardioverter defibrillator (ICD) for prevention of sudden cardiac death. However, they also show an increased risk of ICD-related complications.²⁰⁻²² Therefore, there is an unmet need for accurate risk stratification tools to identify CKD patients at risk of ventricular arrhythmias and sudden cardiac death.

Valvular heart disease in patients with chronic kidney disease

Patients with CKD have an increased risk for developing valvular heart disease, however they are often denied or not referred to surgery due to the increased operative risk.^{23,24} The prognostic implications of untreated severe VHD in the general population are well known, but have not been studied extensively in patients with CKD.²⁵ Underscoring the need of additional studies regarding the prevalence of valvular heart disease in patients with CKD and the frequency of referral for surgical or transcatheter valve intervention.

In CKD patients, valvular calcium is an important underlying mechanism of valve dysfunction. Valvular calcium is associated with an increased risk of all-cause mortality in patients with end-stage renal disease.^{26,27} However, the prognostic implications of left-sided valve calcium in patients with stage 2 and 3 CKD (eGFR of 60-89 mL/min/1.73m² and 30-59 mL/min/1.73m² respectively) are unknown.

Atrial fibrillation in patients with chronic kidney disease

Atrial fibrillation is very common in end-stage renal disease patients and the incidence of newly diagnosed atrial fibrillation in older patients initiating dialysis is 5-fold higher than in the general population.⁹⁻¹¹ Electrical and structural remodeling of the atrial myocardium serves as a substrate for atrial fibrillation.¹² In patients with end-stage renal disease, the metabolic and hemodynamic disturbances associated with dialysis may modulate the atrial fibrillation substrate

contributing to the high incidence of atrial fibrillation.¹³ To date, the structural remodeling of the left atrium has not been characterized in this group of patients.

Outline of the thesis

The aim of this thesis was to evaluate cardiac mechanics using two-dimensional (speckle tracking) echocardiography and coronary computed tomography angiography in patients with CKD to define the prevalence and prognostic implications of cardiovascular diseases.

In **Part I** the value of two-dimensional speckle tracking echocardiography was investigated for assessing LV GLS and LV mechanical dispersion in patients with CKD and its prognostic implications. **Chapter 2** analyses LV GLS, assessed by two-dimensional speckle tracking echocardiography, in pre-dialysis and dialysis patients with preserved LVEF. **Chapter 3** evaluates the prognostic implications of LV GLS in pre-dialysis and dialysis patients. **Chapter 4** discusses the value of LV mechanical dispersion and LV GLS as risk markers of ventricular arrhythmias in pre-dialysis and dialysis patients.

Part II focuses on the prevalence and prognostic implications of valvular heart disease and mitral and aortic valve calcium in patients with CKD. **Chapter 5** investigates the prevalence and prognostic value of valvular heart disease in pre-dialysis and dialysis patients. **Chapter 6** describes the prevalence and prognostic implications of mitral and aortic valve calcium in patients with CKD.

Part III focuses on atrial fibrillation in patients with end-stage renal disease. **Chapter 7** provides more insight on the echocardiographic associates of atrial fibrillation in patients with end-stage renal disease.

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Chapter 2

PREVALENCE OF LEFT VENTRICULAR SYSTOLIC DYSFUNCTION IN PRE-DIALYSIS AND DIALYSIS PATIENTS WITH PRESERVED LEFT VENTRICULAR EJECTION FRACTION

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ABSTRACT

Aims

Patients with chronic kidney disease (CKD) have an excess of cardiovascular morbidity and mortality with heart failure (HF) being particularly frequent. Reduced left ventricular (LV) ejection fraction (EF) defines LV systolic dysfunction and is associated with poor prognosis. However, CKD patients may have HF symptoms with preserved LVEF. In this subgroup of patients, 2-dimensional speckle tracking echocardiography can detect LV systolic dysfunction by analysing LV myocardial deformation. The present study evaluated the prevalence of impaired LV global longitudinal strain (GLS) in CKD patients with preserved LVEF and its prognostic consequences.

Methods and results

Two-hundred pre-dialysis and dialysis patients (65% men, mean age 60 ± 14 years) with CKD stage 3b-5 and preserved LVEF ($\text{LVEF} \geq 50\%$) were evaluated. LV systolic dysfunction despite preserved LVEF was defined by LV GLS $\leq 15.2\%$ (cut-off value derived from the 2 standard deviations below the mean value of individuals without structural heart disease). Impaired LV GLS ($\leq 15.2\%$) despite preserved LVEF was observed in 32% of patients. During a median follow-up of 33 months (IQR; 17,62 months), 47% of patients underwent renal transplantation, 9% were admitted with heart failure and 28% died. Patients with LV GLS $\leq 15.2\%$ showed significantly worse cumulative event-free survival rates of the combined endpoint of HF hospitalisation and all-cause mortality compared to patients with LV GLS $> 15.2\%$ (Log-rank $P=0.018$).

Conclusion

The prevalence of impaired LV GLS despite preserved LVEF in pre-dialysis and dialysis patients is relatively high. Patients with preserved LVEF but impaired LV GLS have an increased risk of HF hospitalisation and all-cause mortality.

INTRODUCTION

Patients with chronic kidney disease (CKD) exhibit an increased risk of cardiovascular morbidity and mortality, with heart failure (HF) hospitalization being one of the most frequent cardiovascular events.¹ Chronic pressure and volume overload as well as non-hemodynamic factors, such as oxidative stress and inappropriate renin-angiotensin-aldosterone system activation, lead to the development of left ventricular (LV) systolic and diastolic dysfunction.² LV ejection fraction (LVEF), calculated from two-dimensional echocardiography, is the most frequently used parameter to define LV systolic (dys)function,³ and is strongly associated with HF and increased mortality in this specific group of patients.^{4,5} However, LVEF has been shown rather insensitive to the detection of LV systolic dysfunction, particularly in patients with CKD. In these patients, LV hypertrophy and changes in the LV structure may lead to subtle LV systolic dysfunction despite preserved LVEF.⁶ LV global longitudinal strain (GLS), assessed with two-dimensional speckle tracking echocardiography, may provide more detailed information on LV systolic function.⁷ The prevalence of subtle LV systolic dysfunction, according to LV GLS in patients with CKD and preserved LVEF is unknown. In addition, data on the prognostic value of LV GLS in this population with preserved LVEF are accumulating.⁸⁻¹⁰ Accordingly, the present study investigated the prevalence of impaired LV GLS in pre-dialysis and dialysis patients with preserved LVEF. Furthermore the relationship between LV GLS and the combined endpoint of HF hospitalization and all-cause mortality and all-cause mortality alone, was investigated.

METHODS

Patient population

From an ongoing registry of pre-dialysis and dialysis patients at the Leiden University Medical Centre, The Netherlands,¹¹ patients with preserved LVEF ($\geq 50\%$) and New York Heart Association functional class I-IV, assessed by transthoracic echocardiography performed during hemodynamic stable conditions, were selected. All patients were diagnosed with chronic kidney disease (CKD) stage 3b-5 according to the 2012 Clinical Practice Guideline for the Evaluation and Management of CKD by Kidney Disease: Improving Global

Outcomes (KDIGO).¹² Patients younger than 18 years old, patients with LVEF <50% or in whom the echocardiography was performed during hospitalization for HF, as well as patients with limited echocardiographic examination or with inadequate image quality for off-line analysis, were excluded. The electronic medical records (HiX; ChipSoft, Amsterdam, The Netherlands) and the departmental cardiology information system (EPD-vision; Leiden University Medical Centre, Leiden, The Netherlands) were reviewed to collect the clinical data. LV GLS was measured with speckle tracking echocardiography. LV systolic dysfunction despite preserved LVEF was defined by a value of LV GLS lower than 2 standard deviations below the mean value of LV GLS derived from individuals without structural heart disease.¹³ Patients were followed-up for the occurrence of HF hospitalization and all-cause mortality at the Leiden University Medical Centre. The institutional review board approved this retrospective analysis of clinically acquired data and waived the need for patient written informed consent.

Clinical characteristics

Demographics, cardiovascular risk factors, medication use and laboratory results were included as baseline clinical variables. Estimated glomerular filtration rate (eGFR) was calculated by the CKD Epidemiology Collaboration (CKD-EPI) equation as recommended.¹² Using the concentration of creatinine in a 24-hour urine specimen and the pre-dialysis plasma creatinine concentration, residual renal function was calculated.¹⁴ Ultrafiltration rate was calculated as follows: mean ultrafiltration volume (mL) of 5 sessions/session duration (hour)/target weight (kg). Delta systolic blood pressure was calculated by subtracting pre-dialysis systolic blood pressure from post-dialysis systolic blood pressure. Estimated GFR was only measured in pre-dialysis patients, while residual renal function, dialysis type and dialysis vintage were measured in dialysis patients and ultrafiltration rate and delta systolic blood pressure in hemodialysis patients.

Transthoracic echocardiography

Two-dimensional transthoracic echocardiography was performed with the patients in the left lateral decubitus position using commercially available systems (Vivid 7 or E9, General Electric Vingmed, Milwaukee, WI, USA) equipped with 3.5 MHz or M5S transducers. The echocardiographic data were digitally stored in cineloop format for off-line analysis (EchoPac 112.0.1, GE Medical Systems, Horten, Norway). From the parasternal long-axis view, linear dimensions of the

left ventricle were measured on M-mode recordings and LV mass was derived from the Devereux formula and indexed to body surface area.³ Using the biplane Simpson's method, LV end-diastolic and end-systolic volumes and LVEF were measured from the apical 4- and 2-chamber views.³ From the apical 4-chamber view, left atrial (LA) volume was measured, using the disk summation technique and indexed for body surface area. Tricuspid annular plane systolic excursion (TAPSE), as a measure of right ventricular function, was assessed in the focused apical 4-chamber view of the right ventricle applying anatomical M-mode.³ By measuring the width of the vena contracta, mitral regurgitation severity was graded semi-quantitatively, from colour-flow Doppler data.¹⁵ Peak early diastolic (E) and late diastolic (A) wave velocities were measured using pulsed wave Doppler recordings of the mitral inflow. Lateral E' wave velocity of the mitral annulus was measured with color-coded tissue Doppler imaging (TDI) in the apical 4-chamber view to assess LV relaxation. The E/E' ratio was derived as a measure of LV filling pressures.¹⁶ To quantify LV GLS, two-dimensional speckle-tracking echocardiography was used on standard routine grayscale images of apical 4-, 2-chamber and long-axis views.¹⁷ LV GLS was provided by the software as the average peak systolic longitudinal strain value of the 3 apical views. Normally, LV GLS is presented as negative values since it indicates the shortening of the myocardium relative to the original length; however the magnitude (absolute value) of LV GLS is presented in this analysis.¹⁷ Patients were divided into two groups according to LV GLS >15.2% (more preserved) and LV GLS ≤15.2% (more impaired), a cut-off value obtained from 2 standard deviations below the mean value of LV GLS derived from healthy controls.¹³

Follow-up

The national death registry and case records were reviewed for the occurrence of all-cause mortality during follow-up. In addition, HF hospitalization during follow-up after the index echocardiography was registered through case record review. Finally, the occurrence of renal transplant during follow-up was recorded since this event impacts significantly on the outcome of these patients.

Statistical analysis

Categorical variables were presented as numbers and percentages and continuous variables as the mean ± standard deviation. Continuous variables without a normal distribution were presented as the median and interquartile

range (IQR). Patients were divided into two groups: LV GLS $>15.2\%$ and LV GLS $\leq 15.2\%$. Categorical variables were compared between the groups using the chi-square test or Fisher's exact test and continuous variables were compared between the groups using the Student's T-test or Mann-Whitney U-test, as appropriate. Correlations between continuous variables were tested with the Pearson correlation test. To explore the independent correlates of reduced LV systolic function (LV GLS $\leq 15.2\%$), multivariate binary logistic regression was applied. Cumulative event-free survival rates for the composite endpoint of all-cause mortality and HF hospitalization and all-cause mortality alone were calculated using the Kaplan-Meier method. Comparisons between patients with LV GLS $>15.2\%$ and patients with LV GLS $\leq 15.2\%$ were performed based on the log-rank test. Univariable and multivariable Cox proportional hazard analyses were performed to evaluate the independent association between LV GLS and the composite endpoint of all-cause mortality and HF hospitalization. A 2-sided P value of <0.05 was considered to be statistically significant. Statistical analyses were performed using the SPSS software (Version 20.0. Armonk, NY: IBM Corp).

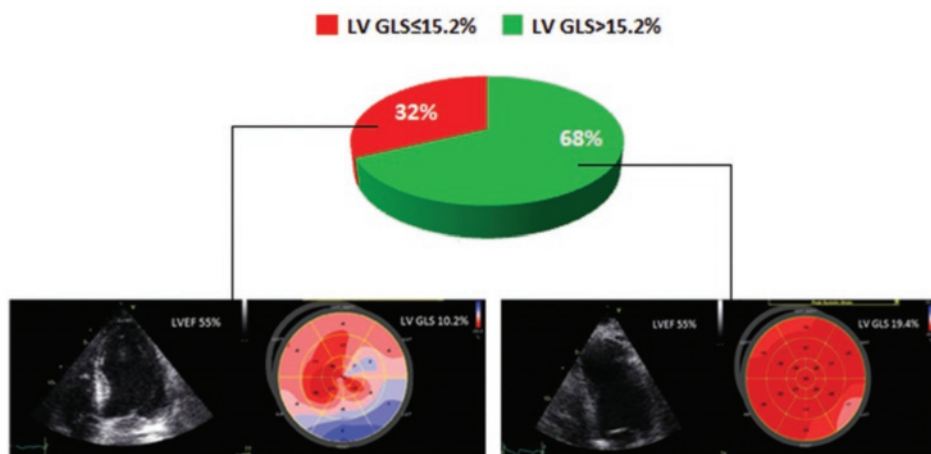


Figure 1. Prevalence of left ventricular (LV) systolic dysfunction based on LV global longitudinal strain (GLS) value $\leq 15.2\%$ in pre-dialysis and dialysis patients with preserved LV ejection fraction (LVEF). Despite LVEF $\geq 50\%$, 32% of patients showed LV systolic dysfunction according to strain analysis. Examples of two patients with and without LV systolic dysfunction are shown in the lower panels: despite having the same LVEF, the patient in the left has severely reduced LV GLS, while the patient in the right shows normal LV GLS.

RESULTS

Patient population

Of 200 pre-dialysis and dialysis patients (65% men, mean age 60 ± 14 years) with LVEF $\geq 50\%$, 136 (68%) had LV GLS $>15.2\%$ and 64 (32%) showed LV GLS $\leq 15.2\%$ (Figure 1). Patients with LV GLS $\leq 15.2\%$ had more advanced CKD, shorter dialysis vintage, higher heart rate and higher prevalence of associated comorbidities compared to patients with LV GLS $>15.2\%$ (Table 1). Furthermore, patients with LV GLS $\leq 15.2\%$ had a higher use of oral anticoagulation and lower albumin level compared to patients with LV GLS $>15.2\%$ (Table 1).

On echocardiography, patients with LV GLS $\leq 15.2\%$ had thicker interventricular septum and posterior wall and larger LV mass index compared to patients with LV GLS $>15.2\%$. LV end-systolic diameter and volume were larger in patients with LV GLS $\leq 15.2\%$ compared to patients with LV GLS $>15.2\%$. As per inclusion criteria all patients had LVEF $\geq 50\%$, however patients with LV GLS $\leq 15.2\%$ showed lower LVEF compared to patients with LV GLS $>15.2\%$ (61% vs. 65% respectively). Early diastolic mitral annular velocity (E') was lower and LV filling pressures were higher in patients with LV GLS $\leq 15.2\%$ compared to their counterparts (Table 2).

Table 1. Characteristics of pre-dialysis and dialysis patients with preserved left ventricular ejection fraction and left ventricular (LV) global longitudinal strain (GLS) $\leq 15.2\%$ versus LV GLS $>15.2\%$

Variable	LV GLS $>15.2\%$ (n=136)	LV GLS $\leq 15.2\%$ (n=64)	P value
<u>Clinical characteristics:</u>			
Age (years)	58 ± 13	62 ± 14	0.107
Male gender	84 (62%)	45 (70%)	0.239
Dialysis (vs. pre-dialysis)	40 (29%)	33 (52%)	0.002
Dialysis type (hemodialysis)*	29 (73%)	27 (82%)	0.349
Dialysis vintage (days)*	185 (89-378)	87 (50-225)	0.040
Ultrafiltration rate (mL/h/kg)#	5.8 (1.6-8.1)	7.0 (3.9-10.1)	0.252
Delta SBP (mmHg)#	4.1 ± 17	0.4 ± 22	0.545
Renal transplantation future	67 (49%)	26 (41%)	0.253
Heart rate (beats per minute)	70 ± 14	75 ± 14	0.023
Systolic blood pressure (mmHg)	137 ± 19	141 ± 23	0.265
Diastolic blood pressure (mmHg)	79 ± 10	77 ± 13	0.400
Body mass index (kg/m ²)	25 ± 4	25 ± 5	0.635
NYHA class III-IV	1 (1%)	3 (5%)	0.103

Table 1. Continued

Variable	LV GLS>15.2% (n=136)	LV GLS≤15.2% (n=64)	P value
Smoker	87 (66%)	35 (57%)	0.253
Diabetes mellitus	29 (21%)	20 (31%)	0.128
Hypertension	118 (87%)	53 (83%)	0.459
Hypercholesterolemia	50 (37%)	23 (36%)	0.910
Previous myocardial infarction	11 (8%)	20 (31%)	<0.001
Previous CABG/PCI	16 (12%)	21 (33%)	<0.001
Peripheral artery disease	9 (7%)	16 (25%)	<0.001
Atrial fibrillation	13 (10%)	9 (14%)	0.342
<u>Medications:</u>			
Diuretics	83 (63%)	42 (66%)	0.757
ACE inhibitor/ARB	85 (65%)	35 (55%)	0.169
B-blocker	69 (53%)	34 (53%)	0.953
Calcium antagonist	64 (49%)	23 (36%)	0.088
Statin	69 (53%)	38 (59%)	0.377
Antiplatelet	37 (28%)	25 (39%)	0.128
Oral anticoagulation	18 (14%)	17 (27%)	0.028
Nitrates	7 (5%)	7 (11%)	0.235
<u>Laboratory results:</u>			
RRF (ml/min/1.73m ²)*	5.8 (2.4-8.6)	5.3 (4.1-7.5)	0.703
eGFR CKD-EPI (mL/min/1.73m ²) †	18 ± 7	18±7	0.942
Creatinine (umol/L) †	320 ± 114	319 ± 117	0.968
Urea (mmol/L)	21 ± 6	22 ± 8	0.553
Corrected calcium (mmol/L)	2.2 ± 0.1	2.3 ± 0.2	0.240
Phosphate (mmol/L)	1.4 ± 0.3	1.4 ± 0.4	0.633
Parathyroid hormone (pmol/L)	15 (7-25)	13 (9-25)	0.847
Albumin (g/L)	42 ± 6	39 ± 6	0.001
Glucose (mmol/L)	6 ± 2	7 ± 3	0.238
LDL-cholesterol (mmol/L)	2.5 ± 1.3	2.3 ± 1.0	0.192
Hemoglobin (mmol/L)	7.2 ± 0.9	7.2 ± 1.1	0.916

*Measured only in dialysis patients. #Measured only in hemodialysis patients. †Measured only in pre-dialysis patients. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RRF, residual renal function; SBP, systolic blood pressure. Continuous data are presented as mean ± SD or median (interquartile range). Categorical data are presented as numbers and percentages.

Table 2. Echocardiographic characteristics of pre-dialysis and dialysis patients with preserved left ventricular ejection fraction and left ventricular (LV) global longitudinal strain (GLS) $\leq 15.2\%$ versus LV GLS $>15.2\%$

Variable	LV GLS $>15.2\%$ (n=136)	LV GLS $\leq 15.2\%$ (n=64)	P value
IVSTd (mm)	10 $\pm$ 2	12 $\pm$ 3	<0.001
PWTd (mm)	10 $\pm$ 2	11 $\pm$ 2	0.003
LVEDD (mm)	50 $\pm$ 7	51 $\pm$ 7	0.145
LV mass index (gm/m ²)	101 $\pm$ 24	129 $\pm$ 46	<0.001
LVESD (mm)	31 $\pm$ 6	33 $\pm$ 8	0.025
LVEDV (ml)	97 $\pm$ 32	104 $\pm$ 39	0.198
LVESV (ml)	34 $\pm$ 14	42 $\pm$ 21	0.003
LVEF (%)	65 $\pm$ 7	61 $\pm$ 9	<0.001
LAVI (mL/m ²)	25 $\pm$ 11	28 $\pm$ 16	0.079
TAPSE (mm)	19 $\pm$ 4	18 $\pm$ 4	0.054
Moderate/severe MR	7 (5%)	6 (9%)	0.356
Peak E-wave velocity (cm/s)	70 $\pm$ 22	77 $\pm$ 32	0.138
Peak A-wave velocity (cm/s)	82 $\pm$ 21	87 $\pm$ 27	0.197
Lateral E' (cm/s)	7 $\pm$ 3	6 $\pm$ 3	0.042
Lateral E/E'	10 (8-14)	13 (9-20)	0.010

GLS, global longitudinal strain; IVSTd, interventricular septum thickness in diastole; LAVI, left atrial volume index; LV, left ventricular; LVEDD, left ventricular end diastolic diameter; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVESV, left ventricular end systolic volume; MR, mitral regurgitation; PWTd, posterior wall thickness in diastole; TAPSE, tricuspid annular plane systolic excursion.

Continuous data are presented as mean $\pm$ SD or median (interquartile range). Categorical data are presented as numbers and percentages.

Independent correlates of LV GLS $\leq 15.2\%$

Table 3 shows the results of the univariate and multivariate analyses. The univariate analysis included variables that were known to influence LV GLS and were significantly different between patients with LV GLS $\leq 15.2\%$ and patients with LV GLS $>15.2\%$. The variables significantly associated with LV GLS $\leq 15.2\%$ at univariate analysis were included in the multivariate analysis. Interventricular septum thickness in diastole, posterior wall thickness in diastole, LV end-systolic

volume and lateral E' wave velocity were not included in the multivariate model to avoid multicollinearity. Only increased heart rate and larger LV mass index were independently associated with LV GLS $\leq 15.2\%$.

Table 3. Clinical and echocardiographic variables associated with left ventricular (LV) global longitudinal strain (GLS) $\leq 15.2\%$ in pre-dialysis and dialysis patients with preserved LV ejection fraction (LVEF)

	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
Dialysis (vs. pre-dialysis)	2.56 (1.38-4.72)	0.003	1.51 (0.60-3.79)	0.381
Dialysis vintage (days)	1.00 (0.999-1.00)	0.508		
Heart rate (bpm)	1.02 (1.003-1.05)	0.028	1.08 (1.04-1.12)	<0.001
Previous MI	5.17 (2.29-11.63)	<0.001	2.91 (0.71-11.92)	0.139
Previous CABG/PCI	3.66 (1.75-7.66)	0.001	2.33 (0.61-8.90)	0.218
PAD	4.70 (1.95-11.36)	0.001	3.13 (0.90-10.96)	0.074
Oral anticoagulation	2.27 (1.08-4.78)	0.031	1.32 (0.39-4.53)	0.657
Albumin (g/L)	0.91 (0.87-0.97)	0.002	0.97 (0.91-1.04)	0.412
IVSTd (mm)	1.33 (1.16-1.54)	<0.001		
PWTd (mm)	1.29 (1.10-1.52)	0.002		
LVESD (mm)	1.06 (1.01-1.11)	0.016	1.02 (0.95-1.09)	0.576
LVESV (mm)	1.03 (1.01-1.05)	0.001	.	
LVEF (%)	0.93 (0.89-0.97)	0.001	0.95 (0.90-1.00)	0.066
Lateral E' (cm/s)	0.89 (0.79-0.997)	0.044		
Lateral E/E'	1.05 (1.01-1.09)	0.014	1.03 (0.98-1.08)	0.265
LV mass index (gm/m ²)	1.03 (1.02-1.04)	<0.001	1.03 (1.01-1.04)	<0.001

BPM, beats per minute; CABG, coronary artery bypass graft; CI, confidence interval; IVSTd, interventricular septum thickness in diastole; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVESV, left ventricular end systolic volume; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; PWTd, posterior wall thickness in diastole; OR, odds ratio.

Prognostic implications of LV systolic dysfunction despite preserved LVEF

A total of 93 (47%) patients underwent renal transplantation, 17 (9%) were admitted with HF and 55 (28%) died during a median follow-up of 33 months (IQR; 17, 62 months). Sixteen patients died of cardiovascular causes. The Kaplan-Meier curves of the composite endpoint of all-cause mortality and HF hospitalization for

patients with LV GLS $\leq 15.2\%$ versus patients with LV GLS $>15.2\%$ are presented in Figure 2. Patients with LV GLS $\leq 15.2\%$ showed significantly worse cumulative event-free survival rates of heart-failure hospitalization and all-cause mortality compared to patients with LV GLS $>15.2\%$ (66% vs 80% at 36-month follow-up, respectively; Log-rank $P=0.018$). When dividing the population according to the cut-off value proposed in current recommendations when using the EchoPac platform³ (LV GLS $<17\%$ vs. $\geq 17\%$) the results remained unchanged.

The Kaplan-Meier curves of all-cause mortality for patients with LV GLS $\leq 15.2\%$ versus patients with LV GLS $>15.2\%$ are presented in Figure 3. Patients with LV GLS $\leq 15.2\%$ showed significantly worse prognosis compared to patients with LV GLS $>15.2\%$; the cumulative event-free survival at 36 months was 71% and 84% respectively (Log-rank $P=0.040$). The number of terminal events for the composite endpoint of all-cause mortality and HF hospitalization and all-cause mortality alone are presented in the Supplemental Table.

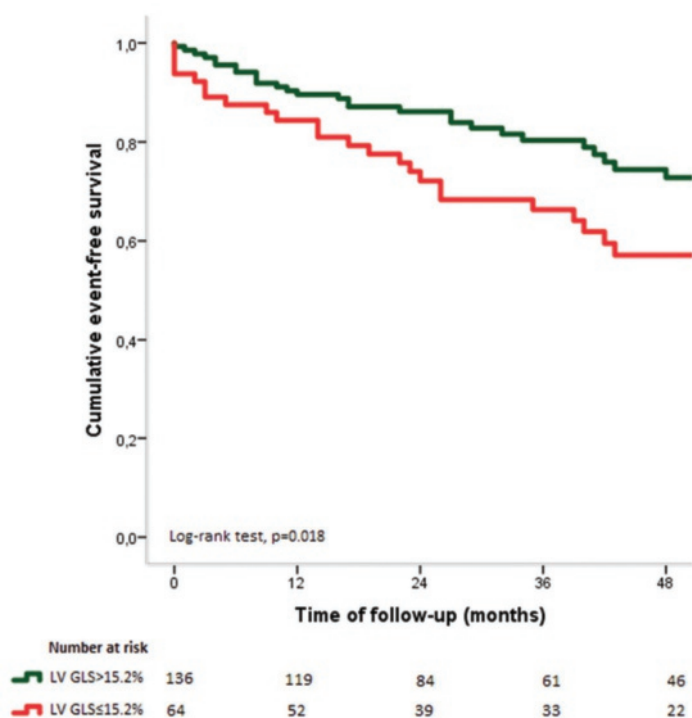


Figure 2. Kaplan-Meier curves of the cumulative event-free survival for the composite endpoint of all-cause mortality and heart failure hospitalization according to left ventricular (LV) global longitudinal strain (GLS) $\leq 15.2\%$ versus LV GLS $>15.2\%$.

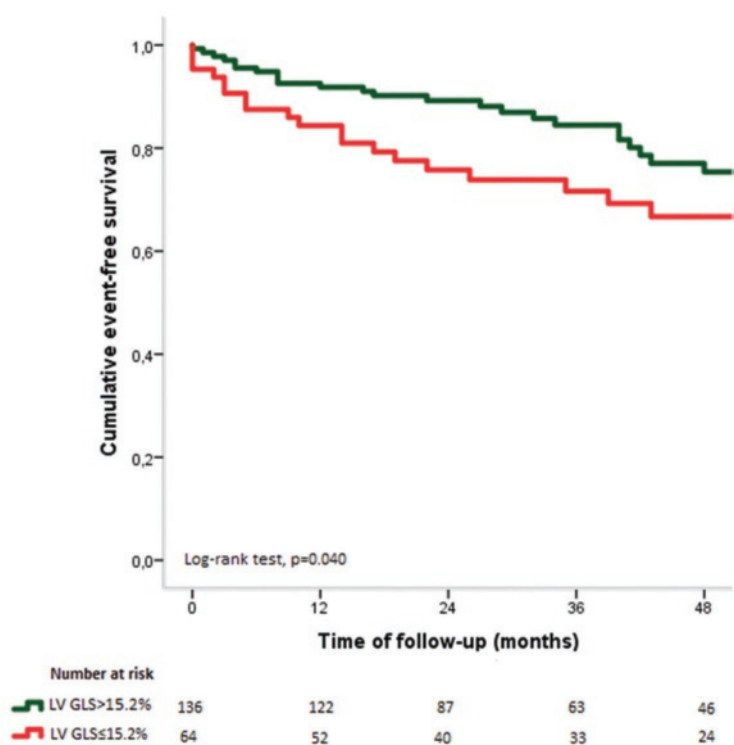


Figure 3. Kaplan-Meier curves of the cumulative event-free survival for all-cause mortality according to left ventricular (LV) global longitudinal strain (GLS) $\leq 15.2\%$ versus LV GLS $>15.2\%$.

On univariable analyses age, renal transplantation, CKD stage, diastolic blood pressure, lateral E/E' and LV GLS were associated with the composite endpoint of all-cause mortality and HF hospitalization (Table 4). On multivariable analysis, LV GLS was independently associated with increased risk of all-cause mortality and HF hospitalization after correcting for age, renal transplantation, CKD stage, diastolic blood pressure, lateral E/E' and LV mass index (Table 4).

DISCUSSION

The present study demonstrates that the prevalence of LV systolic dysfunction as assessed with LV GLS in pre-dialysis and dialysis patients with preserved LVEF is relatively high. Increased heart rate and LV mass index were independently associated with impaired LV GLS. Furthermore, pre-dialysis and dialysis

patients with preserved LVEF but impaired LV GLS exhibit increased rates of HF hospitalisation and all-cause mortality as compared to patients with more preserved LV GLS.

Table 4. Cox proportional hazard model showing the association between clinical and echocardiographic variables and the composite endpoint of all-cause mortality and heart failure (HF) hospitalization in pre-dialysis and dialysis patients with preserved left ventricular ejection fraction (LVEF)

	Univariable HR (95% CI)	P value	Multivariable HR (95% CI)	P value
Age	1.07 (1.05-2.00)	<0.001	1.06 (1.03-1.09)	<0.001
Male gender	1.26 (0.73-2.16)	0.408		
RTx future	0.24 (0.12-0.49)	<0.001	0.44 (0.19-0.98)	0.046
Dialysis (vs. pre-dialysis)	1.79 (1.09-2.95)	0.022	1.57 (0.89-2.76)	0.117
Dialysis vintage (days)	1.00 (1.00-1.00)	0.767		
Systolic BP (mmHg)	1.00 (0.99-1.01)	0.956		
Diastolic BP (mmHg)	0.96 (0.94-0.98)	0.001	0.98 (0.95-0.998)	0.030
Heart rate (bpm)	1.01 (0.997-1.03)	0.106		
Previous MI	1.72 (0.93-3.18)	0.082		
Previous CABG/PCI	1.51 (0.84-2.71)	0.164		
PAD	3.63 (2.00-6.57)	<0.001	1.89 (0.93-3.83)	0.077
LVEF (%)	0.98 (0.95-1.01)	0.192		
Lateral E/E'	1.03 (1.01-1.05)	0.014	1.01 (0.98-1.03)	0.577
LV mass index (gm/m ²)	1.003 (0.997-1.01)	0.318	0.998 (0.989-1.01)	0.567
LV GLS (%)	0.90 (0.83-0.97)	0.004	0.91 (0.83-0.999)	0.047

BP, blood pressure; BPM, beats per minute; CABG, coronary artery bypass graft; CI, confidence interval; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; OR, odds ratio; RTx, renal transplantation.

Impaired LV GLS despite preserved LVEF in CKD patients

Over one third of the patients with CKD and preserved LVEF showed LV systolic dysfunction, defined by LV GLS $\leq$ 15.2%, in the present study. CKD has been previously shown to be independently associated with lower values of LV GLS in patients with HF and preserved LVEF.⁶ The prevalence of reduced LV GLS in patients with CKD and preserved LVEF has not been extensively reported

and varies significantly in previous studies.¹⁸⁻²⁰ Among 88 hemodialysis patients with LVEF $\geq 50\%$ and no significant valvular heart disease, HF or chronic atrial fibrillation, 17% had LV systolic dysfunction, defined by LV GLS $\leq 15\%$.¹⁸ In addition, in 106 patients with a broad range of CKD (varying from stage 1 to 5), LVEF $\geq 55\%$ and no history of cardiovascular diseases or symptoms, 24% had LV systolic dysfunction, defined by LV GLS $< 16\%$.¹⁹ This prevalence was as high as 89% in 48 African American hemodialysis patients with preserved LVEF ($\geq 50\%$) and no significant valvular heart disease when using a cut-off value of LV GLS $< 16\%$ to define LV systolic dysfunction.²⁰ The different cut-off values used to define preserved LVEF and differences in patient characteristics (from racial differences, various stages of CKD, to differences in risk factors and cardiovascular comorbidities) have certainly contributed to the differences in the reported prevalence. In addition, the associated cardiovascular comorbidities (after excluding significant valvar heart disease) and the changing loading conditions of the patients may have contributed to such high prevalence. In the present population, patients with reduced LV GLS more frequently had coronary artery disease, which may have influenced the prevalence of LV systolic dysfunction. In addition, increased heart rate and larger LV mass index were independently associated with LV GLS $\leq 15.2\%$, after adjusting for various clinical and echocardiographic variables. The pressure and volume overload associated with advanced CKD stages and alterations in calcium-phosphate metabolism and sympathetic innervation induce cardiovascular remodelling that affect the heart and vessels. The arterial system is characterized by increased stiffness and reduced compliance that may induce LV hypertrophy while the presence of arteriovenous access conduits leads to a hyperdynamic circulation that increases heart rate.² The underlying pathophysiology is an increase of the extracellular matrix and fibrosis. This cardiovascular remodelling maintains the LVEF in a (supra-) normal range. However, at long-term follow-up, among patients who develop HF symptoms, some may show reduced LVEF while in other patients, LVEF remains within the normal range. The present study shows that LV GLS detects these changes at an early phase of the disease. Therefore, LV GLS may be an important echocardiographic tool to identify patients at elevated risk for future development of HF.

Supplemental Table 1. Number of terminal events for the composite endpoint of all-cause mortality and HF hospitalization and all-cause mortality alone

	Time of follow-up (months)			
Number of terminal events:	12	24	36	48
All-cause mortality and HF hospitalization:				
LV GLS >15.2%	13	5	5	10
LV GLS ≤15.2%	10	6	4	10
All-cause mortality:				
LV GLS >15.2%	10	4	4	11
LV GLS ≤15.2%	10	5	2	9

Prognostic implications of reduced LV GLS in pre-dialysis and dialysis patients with preserved LVEF

Studies evaluating the occurrence of HF hospitalization and all-cause mortality events in patients with CKD with preserved LVEF stratified according to LV GLS are limited.¹⁸⁻²⁰ In a recent study, Liu et al reported higher cumulative all-cause mortality rates in hemodialysis patients with preserved LVEF but LV GLS ≤15% compared to patients with LV GLS >15% (40% vs 15%, Log-rank P=0.001) over a mean follow-up of 26±10 months.¹⁸ In contrast, there were no differences in HF hospitalization events.¹⁸ In a larger population, including a broad range of CKD stages (from 1 to 5), Panoulas et al showed that patients with LV GLS <16% had higher rates of major adverse cardiac events (including all-cause mortality, acute coronary syndromes, stable angina requiring revascularization and HF hospitalization) as compared to patients with LV GLS ≥16% (11% vs 6% at 12-month follow-up, P=0.038).¹⁹ The present study reports on the prevalence and prognostic implications of LV systolic dysfunction despite preserved LVEF in the largest population of pre-dialysis and dialysis patients so far. LV GLS ≤15.2% was associated with increased events for the combined endpoint of HF hospitalization and all-cause mortality as well as for all-cause mortality alone. Prospective studies may answer the question whether implementation of HF therapy on top of optimal control of cardiovascular risk factors at this early stage of LV systolic dysfunction would result in improved outcome.

Limitations

This study has several limitations including its retrospective design and relative small sample size. Since only pre-dialysis and dialysis patients with a clinically indicated echocardiography were included in this analysis, there may be a selection bias. Secondly, pre-dialysis and dialysis patients with a previous myocardial infarction were not excluded. However, any form of coronary artery disease (prior myocardial infarction or prior coronary revascularization) did not affect the independent association between LV GLS $\leq 15.2\%$ and outcome. Furthermore patients with significant valvular heart disease were not excluded, which may have affected LV GLS, although the prevalence of moderate/severe mitral regurgitation was not significantly different between patients with LV GLS $\leq 15.2\%$ and LV GLS $>15.2\%$. In addition, LV GLS may have been influenced by loading conditions, despite the fact that echocardiography was performed after dialysis and ultrafiltration rate and delta systolic blood pressure were not significantly different between patients with LV GLS $\leq 15.2\%$ and LV GLS $>15.2\%$. The low number of cardiovascular mortality events precluded the analysis of the independent association between LV GLS and this endpoint.

Conclusion

In pre-dialysis and dialysis patients with preserved LVEF, the prevalence of LV systolic dysfunction as defined by an LV GLS $\leq 15.2\%$ is as high as 32%. Increased heart rate and LV mass index were independently associated with impaired LV GLS. Pre-dialysis and dialysis patients with preserved LVEF and LV GLS $\leq 15.2\%$ have worse prognosis with significantly higher rates of HF hospitalisation and all-cause mortality as compared with patients with LV GLS $>15.2\%$. LV GLS was independently associated with an increased risk of all-cause mortality and HF hospitalization.

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Chapter 3

PROGNOSTIC IMPLICATIONS OF LEFT VENTRICULAR GLOBAL LONGITUDINAL STRAIN IN PRE-DIALYSIS AND DIALYSIS PATIENTS

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ABSTRACT

Chronic kidney disease (CKD) is a worldwide growing epidemic associated with an increased risk of cardiovascular morbidity and mortality. Left ventricular (LV) global longitudinal strain (GLS) is a measure of LV systolic function associated with prognosis in the general population. However, little is known about the association between LV GLS and survival in patients with CKD. The aim of the present study was to investigate the prognostic implications of LV GLS in pre-dialysis and dialysis patients specifically. LV GLS was measured in a retrospective cohort of pre-dialysis and dialysis patients (CKD stage 3b-5) who underwent clinically indicated echocardiography between 2004 and 2015. Patients were divided into 4 groups according to quartiles of LV GLS: first quartile (LV GLS $\leq$ 10.6%, worst function), second quartile (LV GLS 10.7-15.1%), third quartile (LV GLS 15.2-17.8%) and fourth quartile (LV GLS $\geq$ 17.9%, best function). The primary endpoint was all-cause mortality. Of 304 patients (62 $\pm$ 14 years, 66% male), 65% were in pre-dialysis and 35% in dialysis. During a median follow-up of 29 months (IQR; 16, 58 months), 34% of patients underwent renal transplantation and 36% died. Patients with LV GLS $\leq$ 10.6% showed significantly worse prognosis compared to the other groups (log-rank test, $p<0.001$). LV GLS $\leq$ 10.6% was significantly associated with increased risk of all-cause mortality (HR 2.18, 95% CI 1.17-4.06, $p=0.014$) after correcting for age, gender, albumin levels, atrial fibrillation and renal transplantation. In conclusion, in pre-dialysis and dialysis patients, severely impaired LV GLS is independently associated with an increased risk of mortality.

INTRODUCTION

Chronic kidney disease (CKD) is a worldwide growing epidemic associated with an increased risk of cardiovascular morbidity and mortality.¹⁻⁴ Heart failure is particularly frequent among patients with CKD.² Pressure and volume overload and non-hemodynamic factors associated with CKD induce left ventricular (LV) hypertrophy, reduce capillary density and increase myocardial fibrosis that lead to LV diastolic and systolic dysfunction.⁵ These processes have been proposed as important determinants of increased mortality in this population.⁵ LV global longitudinal strain (GLS) assessed with two-dimensional speckle-tracking echocardiography is a marker of LV systolic function and has been shown to correlate with the extent of myocardial fibrosis.^{6,7} The incremental prognostic value of LV GLS over conventional echocardiographic parameters of LV systolic function such as LV ejection fraction has been demonstrated in patients with various cardiovascular diseases (ischemic heart disease, valvular heart disease and heart failure).⁸ However, little is known about the association between LV GLS and prognosis in patients with CKD. Accordingly the aim of the present study was to investigate the prognostic implications of LV GLS in pre-dialysis and dialysis patients specifically.

METHODS

From a departmental database of pre-dialysis and dialysis patients, those who were clinically referred for transthoracic echocardiography at the Leiden University Medical Centre between 2004 and 2015 were identified and included in this retrospective study. Patients were diagnosed with CKD stage 3b-5 according to the classification of Kidney Disease: Improving Global Outcomes (KDIGO) 2012 Clinical Practice Guideline for the Evaluation and Management of CKD.⁹ Patients younger than 18 years old, with limited echocardiographic examination or with inadequate image quality for off-line analysis, were excluded. Clinical data were collected through review of the electronical medical records (HiX; ChipSoft, Amsterdam, The Netherlands) and the departmental cardiology information system (EPD-vision; Leiden University Medical Centre, Leiden, The Netherlands) and retrospectively analysed. Patients were followed-up for the occurrence of all-cause mortality through case record review and the national

death registry. The occurrence of renal transplantation during follow-up was registered through case record review. The institutional review board approved this retrospective analysis of clinically acquired data.

Baseline clinical variables included demographic parameters, cardiovascular risk factors, medication use and laboratory results. Estimated glomerular filtration rate (eGFR) was calculated by the CKD Epidemiology Collaboration (CKD-EPI) equation.⁹ Residual renal function was calculated by the creatinine clearance using the concentration of creatinine in a 24-hour urine specimen and the pre-dialysis plasma creatinine concentration.¹⁰

Patients were imaged in the left lateral decubitus position using commercially available systems (Vivid 7 or E9, General Electric Vingmed, Milwaukee, WI, USA) equipped with 3.5 MHz or M5S transducers. The echocardiographic data were digitally stored in cineloop format for off-line analysis (EchoPac 112.0.1, GE Medical Systems, Horten, Norway). Linear dimensions of the left ventricle were measured on M-mode recordings from the parasternal long-axis view.¹¹ From the apical 4- and 2-chamber views, the LV end-diastolic and end-systolic volumes were measured according to the biplane Simpson's method and LV ejection fraction was derived.¹¹ Left atrial (LA) volume was measured in the apical 4-chamber view using the disk summation technique and was indexed for body surface area. Right ventricular function was assessed by measuring the tricuspid annular plane systolic excursion (TAPSE) on the focused apical 4-chamber view of the right ventricle applying anatomical M-mode.¹¹ Mitral regurgitation severity was graded semi-quantitatively by measuring the width of the vena contracta from colour Doppler data.¹² Pulsed wave Doppler recordings of the mitral inflow were used to measure peak E (early diastolic) and A (late diastolic) wave velocities. LV relaxation was assessed with color-coded tissue Doppler imaging (TDI) measuring the lateral E' wave velocity of the mitral annulus in the apical 4-chamber view and the E/E' ratio was derived as a measure of LV filling pressures.¹³ LV GLS was measured using two-dimensional speckle-tracking echocardiography on standard routine grayscale images of apical 4-, 2-chamber and long-axis views.¹⁴ Conventionally, LV GLS is presented as negative values since it indicates the shortening of the myocardium relative to the original length.¹⁴ However, the magnitude (absolute value) of LV GLS is presented in this analysis.

Categorical variables were presented as numbers and percentages. Continuous variables with a normal distribution were presented as the mean

$\pm$ standard deviation and those without a normal distribution were presented as the median and interquartile range (IQR). Univariate Cox's proportional hazard analysis was performed to identify the demographic, clinical and echocardiographic variables associated with all-cause mortality. Multivariate survival analysis using Cox's proportional hazard model was used to determine the independent association between LV GLS and all-cause mortality. LV GLS and LV ejection fraction were not included in the same model to avoid multicollinearity. The occurrence of renal transplantation during follow-up was introduced as a time-dependent covariate. Patients were divided into four groups according to quartiles of LV GLS. Cumulative event-free survival rates from the time of echocardiography were calculated using the Kaplan-Meier method and compared across the quartiles of LV GLS. All statistical tests were 2-sided and a P-value of <0.05 was considered statistically significant. Statistical analyses were performed using the SPSS software (Version 20.0. Armonk, NY: IBM Corp).

Table 1. Characteristics of pre-dialysis and dialysis patients

Variable	N=304
<u>Clinical characteristics:</u>	
Age (years)	62 $\pm$ 14
Men	200 (66%)
Chronic kidney disease	
Pre-dialysis	197 (65%)
Dialysis	107 (35%)
Dialysis type (haemodialysis) ¹	82 (77%)
Dialysis vintage (days) ¹	157 (53-357)
Renal transplantation future	104 (34%)
Heart rate (beats per minute)	73 $\pm$ 15
Systolic blood pressure (mmHg)	136 $\pm$ 22
Diastolic blood pressure (mmHg)	77 $\pm$ 12
Body mass index (kg/m ²)	25 $\pm$ 5
NYHA class III-IV	29 (10%)
Smoker	184 (63%)
Diabetes mellitus	90 (30%)
Hypertension	252 (83%)
Hypercholesterolemia	120 (39%)
Previous myocardial infarction	71 (23%)

Table 1. Continued

Previous CABG/PCI	76 (25%)
Peripheral artery disease	52 (17%)
Atrial fibrillation	63 (21%)
<u>Medications:</u>	
Diuretics	198 (67%)
ACE inhibitor/ARB	184 (62%)
Beta-blocker	182 (61%)
Calcium antagonist	119 (40%)
Statin	181 (61%)
Antiplatelet	99 (33%)
Oral anticoagulation	83 (28%)
Nitrates	34 (11%)
<u>Laboratory results:</u>	
Residual renal function (ml/min) ¹	5.3 (2.2-8.9)
eGFR CKD-EPI (mL/min/1.73m ²) ²	18 ± 7
Creatinine (μmol/L) ²	312 ± 116
Urea (mmol/L)	22 ± 7
Corrected calcium (mmol/L)	2.2 ± 0.1
Phosphate (mmol/L)	1.4 ± 0.4
Parathyroid hormone (pmol/L)	16 (8-25)
Albumin (g/L)	41 ± 6
Glucose (mmol/L)	6 ± 3
LDL-cholesterol (mmol/L)	2.4 ± 1.1
Hemoglobin (mmol/L)	7.2 ± 1.0

¹Measured only in dialysis patients. ²Measured only in pre-dialysis patients.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

Continuous data are presented as mean ± SD or median (interquartile range). Categorical data are presented as numbers and percentages.

RESULTS

A total of 304 patients (66% men, mean age 62 ± 14 years) were included. Tables 1 and 2 summarize the clinical and echocardiographic characteristics of the overall patient population. During a median follow-up duration of 29 months (IQR; 16, 58 months), 104 (34%) patients underwent renal transplantation and 108 (36%) patients died. On univariate Cox's proportional hazard analysis, LV GLS and LV ejection fraction were significantly associated with all-cause mortality together with age, male gender, albumin levels, atrial fibrillation and renal transplantation. LV GLS (hazard ratio: 0.96, 95% confidence interval: 0.92-0.998; $P=0.041$) and LV ejection fraction (hazard ratio: 0.99, 95% confidence interval: 0.97-0.997; $P=0.019$) were independently associated with all-cause mortality after correcting for age, male gender, albumin levels, atrial fibrillation and renal transplantation.

Table 2. Echocardiographic characteristics of pre-dialysis and dialysis patients

Variable	N=304
Ventricular septum width (mm)	11 ± 2
Posterior wall width (mm)	10 ± 2
Left ventricular end-diastolic diameter (mm)	53 ± 9
Left ventricular end-systolic diameter (mm)	36 ± 11
Left ventricular end-diastolic volume (ml)	112 ± 53
Left ventricular mass index (gr/m^2)	114 ± 36
Left ventricular end-systolic volume (ml)	54 ± 45
Left ventricular ejection fraction (%)	56 ± 16
Left atrial volume index (mL/m^2)	29 ± 15
TAPSE (mm)	18 ± 5
Moderate/severe mitral regurgitation	45 (15%)
Peak E-wave velocity (cm/s)	78 ± 31
Peak A-wave velocity (cm/s)	80 ± 26
Lateral E' (cm/s)	6 ± 3
Lateral E/E'	12 (8-19)
Left ventricular global longitudinal strain (%)	14 ± 5

TAPSE, tricuspid annular plane systolic excursion.

Continuous data are presented as mean $\pm$ SD or median (interquartile range). Categorical data are presented as numbers and percentages.

Patients were divided into four groups according to quartiles of LV GLS: first quartile (LV GLS $\leq$ 10.6%, worst function), second quartile (LV GLS 10.7-15.1%), third quartile (LV GLS 15.2-17.8%) and fourth quartile (LV GLS $\geq$ 17.9%, best function). Kaplan-Meier curves of the cumulative event-free survival for the different quartiles of LV GLS are presented in Figure 1. Patients with LV GLS $\leq$ 10.6% (most impaired LV systolic function) showed significantly worse prognosis compared to the other groups (log-rank chi-square=31.17, $P<0.001$). Importantly, patients within the lowest LV GLS quartile (LV GLS $\leq$ 10.6%) were less frequently recipients of renal transplantation (8% compared to 32% in patients with LV GLS 10.7-15.1%, 49% in patients with LV GLS 15.2-17.8% and 47% in patients within the highest LV GLS quartile $\geq$ 17.9%). On multivariate analysis, LV GLS $\leq$ 10.6% was independently associated with increased risk of all-cause mortality after correcting for age, gender, albumin levels, atrial fibrillation and renal transplantation as time-dependent covariate (Table 3).

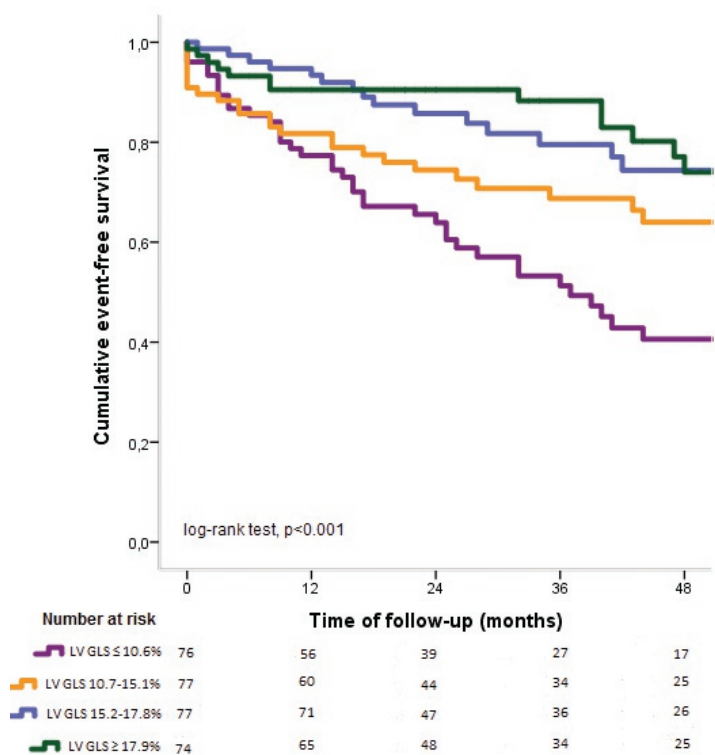


Figure 1. Kaplan-Meier curves of the cumulative event-free survival according to the LV GLS quartile. The cumulative survival rates were compared between the different quartiles of left ventricular (LV) global longitudinal strain (GLS).

Table 3. Association between LV GLS and all-cause mortality: Cox proportional hazard model

	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)	P-value
Renal transplantation	0.08 (0.04-0.15)	<0.001	0.31 (0.15-0.66)	0.002
Age (years)	1.07 (1.05-1.09)	<0.001	1.05 (1.03-1.07)	<0.001
Men	1.26 (0.83-1.90)	0.279	1.02 (0.67-1.57)	0.917
Albumin (g/L)	0.90 (0.87-0.93)	<0.001	0.89 (0.86-0.92)	<0.001
Atrial fibrillation	2.06 (1.35-3.13)	0.001	1.15 (0.73-1.80)	0.542
LV GLS (versus $\geq 17.9\%$)				
15.2-17.8%	1.41 (0.71-2.79)	0.323	1.80 (0.91-3.59)	0.094
10.7-15.1%	2.12 (1.12-4.01)	0.021	1.38 (0.72-2.64)	0.328
$\leq 10.6\%$	4.00 (2.19-7.31)	<0.001	2.18 (1.17-4.06)	0.014

CI, confidence interval; GLS, global longitudinal strain; HR, hazard ratio; LV, left ventricular.

DISCUSSION

CKD is associated with structural and functional LV remodeling as a consequence of pressure and volume overload and non-hemodynamic factors.⁵ Pressure overload is the result of chronic hypertension and vascular stiffness, while anaemia, arteriovenous fistulas and sodium and water retention lead to volume overload.¹⁵ To keep LV wall stress close to normal, the left ventricle responds to pressure and volume overload with hypertrophy and dilatation.¹⁵ As LV hypertrophy progresses, the interstitial space also increases with accumulation of collagen (interstitial or replacement fibrosis) potentially causing a reduction in contractility. In addition, LV hypertrophy increases the myocardial oxygen demand, which causes myocardial hypoperfusion, cardiomyocyte loss and further interstitial fibrosis.^{15,16} Furthermore, non-hemodynamic factors associated with CKD such as inappropriate renin-angiotensin-aldosterone system activation, oxidative stress, inflammation and stimulation of prohypertrophic and profibrogenic factors also contribute to LV remodeling.^{5,15} These structural changes cause impaired LV contractility, which can be detected with LV GLS. Several studies have demonstrated the correlation between LV GLS and the extent of myocardial fibrosis.^{6,7} In a recent study, Kramann et al.⁷ showed that LV strain parameters were significantly associated with the grade of myocardial fibrosis in rat models with uremic cardiomyopathy. The larger the

extent of myocardial fibrosis, the more impaired the value of LV GLS. In addition, it has been shown that LV GLS is a more sensitive marker of LV systolic dysfunction than LV ejection fraction.¹⁷ Patients with LV hypertrophy and preserved LV ejection fraction may show impaired LV GLS in various clinical scenarios indicating that LV GLS better reflects the true damage of the LV myocardium as compared to LV ejection fraction.¹⁸ In the present study, the mean LV ejection fraction was >50% in the majority of pre-dialysis and dialysis patients. However, mean LV GLS was significantly reduced suggesting that the LV contractility is significantly reduced probably because of ongoing LV remodeling with increased fibrosis formation.

The prognostic value of LV GLS has been demonstrated in several clinical scenarios, including patients with preserved LV ejection fraction.^{8,19,20} However, the evidence correlating LV GLS and prognosis in patients with CKD is limited.^{7,21,22} In a recent study, including 171 dialysis patients, LV GLS was independently associated with all-cause mortality (hazard ratio: 1.10, 95% confidence interval: 1.03-1.17; $P<0.01$).⁷ In addition, in 447 patients with a wide range of estimated GFR, LV GLS was independently associated with all-cause mortality (hazard ratio: 1.08, 95% confidence interval: 1.01-1.15; $P=0.03$).²¹ Similar results were observed in a study including 183 patients with stage 4 and 5 CKD, where LV GLS was independently associated with all-cause mortality (hazard ratio: 1.09, 95% confidence interval: 1.02-1.16; $P=0.01$).²² The present study, with the largest cohort of pre-dialysis and dialysis patients so far, demonstrates that patients within the lowest quartile of LV GLS showed worse prognosis compared to the other groups and LV GLS $\leq$ 10.6% was associated with two-fold increased risk of all-cause mortality after correcting for renal transplantation. This is clinically relevant since renal transplantation is considered a life-saving treatment in these patients and proper selection of patients receiving a renal transplant is crucial to optimize the results of this therapy. Whether LV GLS improves after renal transplantation has not been evaluated.

Several limitations should be acknowledged. First, this was an observational, retrospective study. In addition, only pre-dialysis and dialysis patients from the departmental database were included in the present study, after having a clinically indicated echocardiography, introducing a potential selection bias. Furthermore, echocardiography was performed after dialysis therapy, where LV GLS may have been affected by changes in loading conditions.

In pre-dialysis and dialysis patients, severely impaired LV GLS was independently associated with worse prognosis, even after correction for renal transplantation.

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Chapter 4

LEFT VENTRICULAR MECHANICAL DISPERSION AND VENTRICULAR ARRHYTHMIAS IN PRE-DIALYSIS AND DIALYSIS PATIENTS

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ABSTRACT

Background

Patients with advanced chronic kidney disease (CKD) have high risk of sudden cardiac death (SCD) and may benefit from an implantable cardioverter defibrillator (ICD). However, the risk of ICD-related complications is also high in this population. Therefore, there is an unmet need for accurate risk stratification tools to identify CKD patients at risk of ventricular arrhythmias (VA), who may benefit from ICD implantation. This hypothesis generating study aimed to investigate the association between left ventricular (LV) mechanical dispersion and LV global longitudinal strain (GLS) measured with two-dimensional speckle tracking echocardiography and VA and SCD in CKD patients.

Methods

Patients with CKD stage 3b-5 (*estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73m² or on dialysis*) were included and were divided in two groups according to the occurrence of VA or SCD during follow-up. LV mechanical dispersion, as a measure of the temporal heterogeneity of the LV deformation, was measured as the standard deviation of time to peak longitudinal strain of 17 LV segments. The ability of LV mechanical dispersion, LV ejection fraction and LV GLS to discriminate patients with VA or SCD during follow-up was evaluated using receiver operating characteristic curve analysis.

Results

Of 250 patients (66% men, mean age 61±14 years), 16 (6%) patients experienced VA or SCD during a median follow-up duration of 28 months (IQR 16; 53 months). Using receiver operating characteristic curve analyses, LV GLS (area under the curve [AUC]: 0.79, 95% confidence interval [CI]: 0.68-0.89) and LV mechanical dispersion (AUC: 0.71, 95% CI: 0.61-0.82) showed modest discrimination to identify the patients at risk of VA or SCD. In contrast, LV ejection fraction showed poor discrimination (AUC: 0.60, 95% CI: 0.41-0.78).

Conclusion

LV mechanical dispersion along with LV GLS may be an additional valuable risk marker of VA and SCD in pre-dialysis and dialysis patients.

INTRODUCTION

Patients with advanced chronic kidney disease (CKD), particularly dialysis patients, have a high mortality rate.¹ Cardiac disease is the major cause of death and sudden cardiac death (SCD) is the most frequent cause.¹ The enhanced arrhythmogenicity in advanced CKD patients is due to the increased prevalence of cardiac risk factors such as coronary artery disease, left ventricular (LV) hypertrophy and myocardial fibrosis, as well as non-cardiac (CKD-specific) risk factors such as electrolyte alterations, sympathetic hyperactivity, uremia and anemia.² Patients with advanced CKD may benefit from an implantable cardioverter defibrillator (ICD) for prevention of SCD. However, they also show an increased risk of ICD-related complications.³⁻⁵ Therefore, there is an unmet need for accurate risk stratification tools to identify CKD patients at risk of ventricular arrhythmias (VA) and SCD. LV mechanical dispersion and LV global longitudinal strain (GLS), measured with two-dimensional speckle tracking echocardiography, have shown to be associated with VA in several cardiomyopathies.⁶⁻⁸ This hypothesis generating study aimed to investigate the association between LV mechanical dispersion and LV GLS (measured with speckle tracking echocardiography) and VA and SCD in pre-dialysis and dialysis patients.

METHODS

Patient population and protocol

In this retrospective study, pre-dialysis and dialysis patients from an ongoing registry at the Leiden University Medical Centre (The Netherlands) were included.⁹ All patients were diagnosed with CKD stage 3b-5 (estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73m² or on dialysis) according to the classification of the 2012 Clinical Practice Guideline for the Evaluation and Management of CKD from Kidney Disease: Improving Global Outcomes (KDIGO).¹⁰ Patients younger than 18 years old, with inadequate echocardiographic image quality for off-line analysis or with limited echocardiographic examination, were excluded. From the departmental cardiology information system (EPD-vision; Leiden University Medical Centre, Leiden, The Netherlands) and electronical medical records (HiX; ChipSoft, Amsterdam, The Netherlands), clinical data (demographics, cardiovascular risk factors, medication use and laboratory results) were collected

and retrospectively analysed. eGFR was calculated by the CKD Epidemiology Collaboration (CKD-EPI) equation.¹⁰ Residual renal function in dialysis patients was calculated using the pre-dialysis plasma creatinine concentration and the concentration of creatinine in a 24-hour urine specimen.¹¹ QT interval was corrected for heart rate using Bazett's formula.¹² The current retrospective evaluation of clinically acquired data was approved by the institutional review board.

Transthoracic echocardiography

Images were obtained from two-dimensional transthoracic echocardiography with patients lying in the left lateral decubitus position, using commercially available systems (Vivid 7 or E9, General Electric Vingmed, Milwaukee, WI, USA) equipped with 3.5 MHz or M5S transducers. The echocardiographic data were digitally stored in cine-loop format for off-line analysis (EchoPac 112.0.1, GE Medical Systems, Horten, Norway). Linear dimensions of the left ventricle were measured from the parasternal long-axis view on M-mode recordings and LV mass index was calculated and indexed to body surface area.¹³ LV ejection fraction (LVEF) was measured using LV end-diastolic and end-systolic volume from the apical 4- and 2- chamber views, according to the biplane Simpson's method.¹³ To measure wall motion score index (WMSI), the LV was divided into 16 segments and the sum of the segment scores divided by 16 was calculated.¹³ Left atrial volume was measured using the disk summation technique in the apical 4-chamber view and indexed for body surface area.¹³ By measuring the width of the vena contracta in the parasternal long-axis view the severity of mitral regurgitation (MR) was graded semi-quantitatively.¹⁴ The aortic regurgitation was graded according to an integrative approach that includes qualitative (valve morphology, regurgitant jet characteristics, presence of diastolic flow reversal in descending aorta), semi-quantitative (vena contracta width and pressure half time of the continuous wave spectral signal of aortic regurgitation jet) and quantitative parameters (effective regurgitant orifice area and regurgitant volume) as well as LV dimensions.¹⁴ The aortic valve stenosis grade was based on aortic valve area, aortic jet peak velocity and the mean transvalvular gradient measured according to current recommendations.¹⁵ LV diastolic parameters, including peak early diastolic (E) wave and late diastolic (A) wave were measured using pulsed wave Doppler recordings of the mitral inflow and E/A ratio was calculated. Septal and lateral e' mitral annulus velocities were measured with tissue Doppler imaging

at the septal and lateral side of the mitral annulus in the apical 4-chamber view.¹⁶ The e' velocity was calculated by averaging the septal and lateral e' mitral annulus velocities. The E/e' ratio as a measure of LV filling pressures was calculated.¹⁶ Tricuspid regurgitation (TR) gradient was measured on continuous wave Doppler tracings of the tricuspid valve and TR velocity was calculated.¹⁶

Two-dimensional speckle-tracking echocardiography was used to measure LV GLS on standard routine grayscale images of the apical 4-, 2-chamber and long-axis views.¹⁷ LV GLS was derived from the average peak systolic longitudinal strain value of the 3 apical views. LV GLS is normally presented as negative values since it indicates the shortening of the myocardium relative to the original length.¹⁷ However, in the present study, the absolute value of LV GLS is presented. LV mechanical dispersion was measured as the standard deviation of time to peak longitudinal strain of 17 LV segments and represents the temporal heterogeneity of the LV deformation (Figure 1).⁷ The onset of Q/R wave on the surface electrocardiogram was considered to measure the time to peak longitudinal strain.⁷ The interobserver variability of LV mechanical dispersion measurements was evaluated using the Bland-Altman analysis which showed a mean bias was -6.6 ms (95% limits of agreement -42.5 to 29.4 ms).

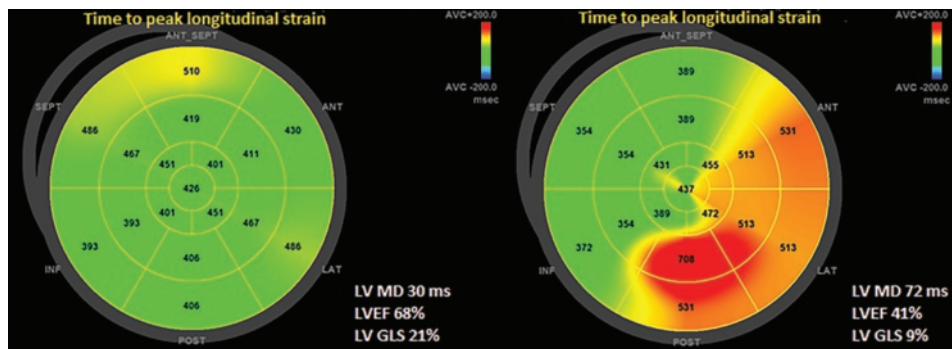


Figure 1. Bull's eye plots of time to peak longitudinal strain in two pre-dialysis patients using a 17-segment model of the left ventricle. The left panel demonstrates a pre-dialysis patient without ventricular arrhythmia or sudden cardiac death during follow-up and left ventricular (LV) mechanical dispersion (MD) of 30 ms, LV ejection fraction (LVEF) of 68% and LV global longitudinal strain (GLS) of 21% (absolute value). The right panel shows a more pronounced LV MD of 72 ms, LVEF of 41% and LV GLS of 9% in a pre-dialysis patient with sustained ventricular tachycardia during follow-up. ANT, anterior; AVC, aortic valve closure; INF, inferior; LAT, lateral; POST, posterior; SEPT, septal.

Follow-up

The occurrence of VA or SCD during follow-up was registered through case record review. VA was defined as aborted cardiac arrest, documented sustained ventricular tachycardia or ventricular fibrillation. Ventricular tachycardia was defined as sustained when lasting longer than 30 seconds or requiring earlier intervention due to haemodynamic instability.¹⁸ SCD was diagnosed when a congenital or acquired potentially fatal cardiac condition was known to be present during life, or autopsy had identified a cardiac or vascular anomaly as the probable cause of the event, or no obvious extra-cardiac causes had been identified by post-mortem examination and therefore an arrhythmic event is a likely cause of death.¹⁹

Statistical analysis

Categorical data are presented as frequencies and percentages and continuous data as mean $\pm$ standard deviation and median with interquartile range (IQR), as appropriate. Patients were divided into two groups according to the occurrence of VA or SCD during follow-up. Student's t-test or Mann-Whitney U-test were used to analyse differences between the two groups for continuous data and chi-square test or Fisher's exact test for categorical data, as appropriate. The ability of LV mechanical dispersion, LVEF and LV GLS to discriminate between patients with and without VA or SCD during follow-up was assessed with receiver operating characteristic (ROC) curves and area under the curve (AUC) was reported. Comparisons between ROC curves of LV mechanical dispersion, LVEF and LV GLS were performed with MedCalc software (version 16.2.1, Ostend, Belgium) using the method of DeLong et al.²⁰ All statistical tests were two sided and a P-value of <0.05 was considered to indicate significance. SPSS software (Version 20.0. Armonk, NY: IBM Corp) was used to perform statistical analyses.

Table 1. Characteristics of pre-dialysis and dialysis patients with and without ventricular arrhythmias or sudden cardiac death during follow-up

Variable	Patients without VA or SCD (n=234)	Patients with VA or SCD (n=16)	P value
<u>Clinical characteristics:</u>			
Age (years)	61 ± 14	62 ± 15	0.785
Male gender, n (%)	150 (64)	14 (88)	0.057
Dialysis (vs. predialysis), n (%)	77 (33)	6 (38)	0.706
Dialysis type (HD), n (%) ¹	56 (73)	5 (83)	1.000
Dialysis vintage, (days) ¹	147 (51-329)	366 (109-724)	0.264
Renal transplantation future, n (%)	87 (37)	4 (25)	0.327
Systolic BP (mmHg)	138 ± 22	122 ± 15	0.007
Diastolic BP (mmHg)	78 ± 12	69 ± 10	0.006
Body mass index (kg/m ²)	25 ± 4	27 ± 6	0.038
NYHA class III-IV, n (%)	18 (8)	1 (6)	1.000
Diabetes mellitus, n (%)	64 (27)	6 (38)	0.395
Hypertension, n (%)	197 (84)	13 (81)	0.727
Hypercholesterolemia, n (%)	88 (38)	7 (44)	0.624
Previous MI, n (%)	49 (21)	7 (44)	0.057
Previous CABG/PCI, n (%)	50 (21)	7 (44)	0.059
Peripheral artery disease, n (%)	37 (16)	6 (38)	0.038
<u>Medications:</u>			
ACE inhibitor/ARB, n (%)	150 (66)	7 (44)	0.075
B-blocker, n (%)	134 (59)	13 (81)	0.076
Calcium antagonist, n (%)	94 (41)	5 (31)	0.432
<u>Laboratory results:</u>			
RRF (ml/min/1.73m ²) ¹	5.5 (2.5-9.2)	3.6 (0.0-8.6)	0.501
eGFR CKD-EPI (mL/min/1.73m ²) ²	18 ± 7	16 ± 5	0.257
Creatinine (umol/L) ²	314 ± 114	352 ± 132	0.315
Urea (mmol/L)	22 ± 7	23 ± 6	0.533
Corrected calcium (mmol/L)	2.2 ± 0.1	2.3 ± 0.1	0.192
Phosphate (mmol/L)	1.4 ± 0.3	1.6 ± 0.5	0.046
Parathyroid hormone (pmol/L)	16 (8-25)	21 (17-22)	0.198
Albumin (g/L)	41 ± 6	43 ± 5	0.256
Hemoglobin (mmol/L)	7.2 ± 1.0	7.7 ± 0.5	0.001

Table 1. Continued

Variable	Patients without VA or SCD (n=234)	Patients with VA or SCD (n=16)	P value
<u>Electrocardiogram:</u>			
QRS duration (ms)	107 ± 25	137 ± 41	0.010
Corrected QT interval (ms)	421 ± 35	443 ± 50	0.100

¹Measured only in dialysis patients.² Measured only in predialysis patients.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CABG, coronary artery bypass graft; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; HD, hemodialysis; MI, myocardial infarction; MS, milliseconds; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RRF, residual renal function; SCD, sudden cardiac death; VA, ventricular arrhythmias.

Continuous data are presented as mean ± SD or median (interquartile range). Categorical data are presented as numbers and percentages.

RESULTS

Of 250 pre-dialysis and dialysis patients (66% men, mean age 61 ± 14 years), 16 (6%) patients experienced VA (n=11) or SCD (n=5) during a median follow-up of 28 months (IQR 16; 53 months). Patients presenting with VA or SCD had a lower systolic and diastolic blood pressure, a higher body mass index, more frequently showed peripheral artery disease, a higher phosphate and haemoglobin level and longer QRS duration compared to patients without VA or SCD during follow-up (Table 1). On echocardiography, patients with VA or SCD had larger LV mechanical dispersion, more impaired LV GLS and larger WMSI compared to their counterparts. LVEF was not significantly different between patients with and without VA or SCD (Table 2, Figure 2). On ROC curve analysis, LV mechanical dispersion and LV GLS showed modest discrimination to identify patients presenting with VA or SCD: AUC 0.71 (95% confidence interval 0.61-0.82) and AUC 0.79 (95% confidence interval 0.68-0.89), respectively. The AUC of LVEF was 0.60 (95% confidence interval 0.41-0.78) suggesting limited discriminative value (Figure 3). The AUC and 95% confidence interval for WMSI was 0.74 (95% confidence interval 0.60-0.88). The AUC of LV GLS was significantly higher than the AUC of LVEF (P=0.016, 95% confidence interval 0.03-0.34), the other AUC values were not significantly different from each other.

Table 2. Echocardiographic characteristics of pre-dialysis and dialysis patients with and without ventricular arrhythmias or sudden cardiac death during follow-up

Variable	Patients without VA or SCD (n=234)	Patients with VA or SCD (n=16)	P value
LVEDV (ml)	110 ± 47	155 ± 102	0.101
LVESV (ml)	50 ± 39	89 ± 91	0.109
LV mass index (gm/m ²)	115 ± 36	128 ± 40	0.195
LVEF (%)	57 ± 14	51 ± 23	0.281
Wall motion score index	1.0 (1.0-1.0)	1.3 (1.0-1.8)	<0.001
LAVI (mL/m ²)	28 ± 15	30 ± 12	0.560
Moderate/severe MR, n (%)	31 (13)	4 (25)	0.253
Moderate/severe AR, n (%)	14 (6)	1 (6)	1.000
Moderate/severe AS, n (%)	18 (8)	2 (13)	0.373
E/A ratio	1.0 ± 0.6	1.2 ± 0.6	0.172
E/e' ratio	15 ± 10	19 ± 8	0.097
TR velocity (m/s)	2.6 ± 0.4	2.5 ± 0.4	0.470
LV GLS (%)	15 ± 5	10 ± 4	<0.001
LV mechanical dispersion (ms)	52 (43-65)	66 (55-74)	0.004

AR, aortic regurgitation; AS, aortic stenosis; GLS, global longitudinal strain; LAVI, left atrial volume index; LV, left ventricular; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end systolic volume; MR, mitral regurgitation; SCD, sudden cardiac death; TR, tricuspid regurgitation; VA, ventricular arrhythmia.

Continuous data are presented as mean ± SD or median (interquartile range). Categorical data are presented as numbers and percentage.

DISCUSSION

The present study demonstrated a frequency of VA and SCD of 6% in pre-dialysis and dialysis patients during follow-up. Interestingly, LVEF was not significantly different between patients with and without VA or SCD. On the contrary, LV GLS was significantly more impaired and LV mechanical dispersion was significantly longer among patients with VA or SCD as compared to patients without. LV GLS and LV mechanical dispersion showed modest discrimination to identify patients presenting with VA or SCD.

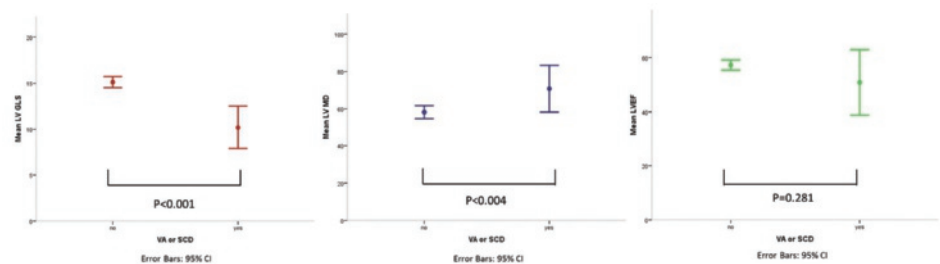


Figure 2. Box plots of left ventricular (LV) global longitudinal strain (GLS), LV mechanical dispersion (MD) and LV ejection fraction (LVEF) in pre-dialysis and dialysis patients with and without ventricular arrhythmia (VA) or sudden cardiac death (SCD) during follow-up. Absolute LV GLS was significantly lower and LV MD significantly higher in patients with VA or SCD compared with patients without VA or SCD during follow-up. LVEF did not significantly differ between patients with and those without VA or SCD during follow-up.

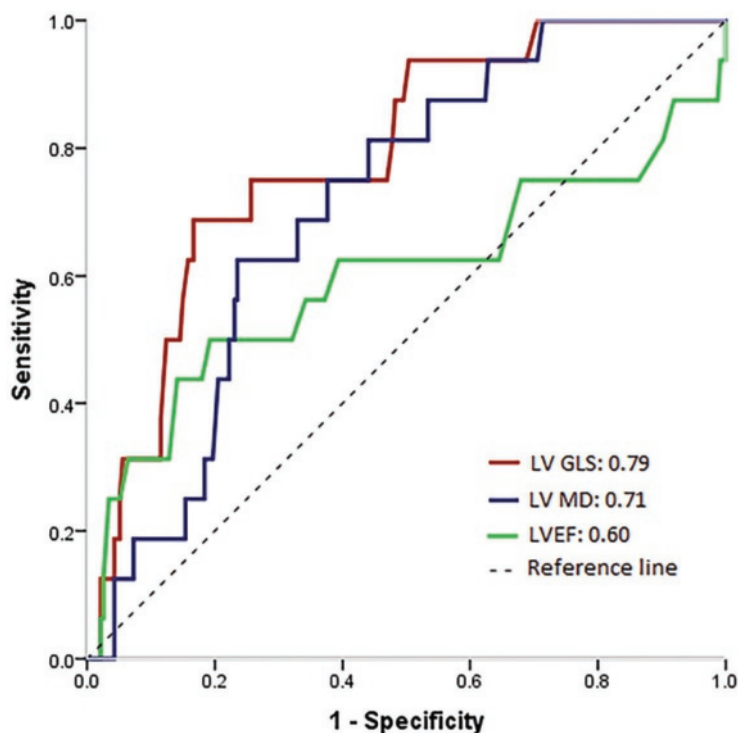


Figure 3. Receiver operating characteristic curve analysis demonstrating the ability of left ventricular (LV) mechanical dispersion (MD), LV ejection fraction (LVEF) and LV global longitudinal strain (GLS) to predict ventricular arrhythmia (VA) or sudden cardiac death (SCD) in pre-dialysis and dialysis patients. Area under the curve and 95% confidence interval (CI) for LV GLS, LV MD and LVEF to discriminate between patients with and without VA or SCD were, respectively, 0.79 (95% CI 0.68-0.89); 0.71 (95% CI 0.61-0.82); 0.60 (95% CI 0.41-0.78).

SCD in CKD patients

SCD accounts for 64% of all cardiac deaths of patients in hemodialysis.¹ In non-dialysis advanced CKD patients, SCD accounts for 16% of all deaths.²¹ The association between CKD and SCD is multifactorial.²² From the Hemodialysis (HEMO) study including 1,745 patients undergoing long-term hemodialysis, age, diabetes, peripheral vascular disease, ischemic heart disease and alkaline phosphatase were independent predictors of SCD.²³ Chronic inflammatory status also contributes to the excess risk of SCD. In the Choices for Healthy Outcomes In Caring for End-stage renal disease (CHOICE) cohort, which included 1,041 incident dialysis patients, high levels of high-sensitive C-reactive protein and interleukin-6 were independently associated with twice the risk of SCD.²⁴ Furthermore, reduced serum albumin was associated with 1.35 times increased risk of SCD. Among 1,078 pre-dialysis patients, Caravaca et al showed that older age and increased comorbidity index (based on aggregation of comorbidities: mild [index 0]= no associated comorbidities, moderate [index 1]= 1 or 2 comorbidities and severe [index 3]= 3 or more comorbidities) were independently associated with increased risk of SCD whereas the use of antiplatelet drugs was associated with reduced risk.²¹ These studies did not include echocardiographic parameters that reflect structural myocardial changes that lead to a vulnerable myocardial substrate in patients with CKD and where transient triggers like ischemia and rapid electrolyte shifts may increase the risk of SCD and VA.^{22,25} Currently, LVEF $\leq 35\%$ is the echocardiographic parameter that American and European guidelines use to recommend ICD implantation for primary prevention of SCD in heart failure patients.^{19,26}

Selection of CKD for ICD implantation: role of advanced echocardiography

The present study provides important novel information on the risk of VA and SCD in pre-dialysis and dialysis patients. First, although LVEF $\leq 35\%$ and heart failure symptoms are main criteria to recommend ICD implantation as primary prevention, this specific group of patients show relatively preserved LVEF.¹⁹ A recent study showed that 81% of hemodialysis patients fulfil criteria for heart failure with preserved LVEF.²⁷ SCD accounts for 30-40% of cardiovascular related deaths among patients with heart failure and preserved LVEF.²⁸ This highlights the need for more sensitive parameters than LVEF that may identify patients at risk of SCD and VA.

LV GLS has demonstrated to be associated with SCD and VA and had incremental predictive value over LVEF in several cardiovascular conditions.^{29,30} LV GLS frequently unmask LV myocardial damage that LVEF cannot detect. In patients with CKD, LV GLS may show LV systolic dysfunction in 30% of patients with preserved LVEF.^{31,32} LV GLS has been associated with increased extent of myocardial fibrosis in anatomopathological autopsy studies, as well as in patients using late gadolinium contrast-enhanced cardiovascular magnetic resonance imaging.^{33,34} Fibrous myocardial tissue intermingled with viable myocardium probably forms the substrate for VA. The present study showed that LV GLS could identify pre-dialysis and dialysis patients at risk of VA and SCD with an AUC larger than that of LVEF indicating that LV GLS may be a superior marker of arrhythmogenic risk.

Furthermore, the mixture of scar or fibrous tissue within layers of viable myocardium enhances the degree of nonuniform anisotropy, increases the risk of electric uncoupling and creates areas of conduction block and slow conduction.³⁵ This pronounced heterogeneous activation can be detected with 2-dimensional speckle tracking and the measurement of LV mechanical dispersion. The association between LV mechanical dispersion and increased risk of VA has been demonstrated in various populations. In 988 patients after acute myocardial infarction, Ersboll et al showed that each increment of 10 ms in LV mechanical dispersion was associated with a 1.15 times increase in the risk of VA.³⁶ In 150 patients with hypertrophic cardiomyopathy, LV mechanical dispersion was independently associated with VA.³⁷ Myocardial infarction patients and hypertrophic cardiomyopathy patients have increased myocardial fibrosis which may enhance the electrical heterogeneity of the LV myocardium. In the present study, LV mechanical dispersion was significantly longer in patients with VA or SCD during follow-up compared to patients without, probably indicating more areas of slow conduction in the former patients. LV mechanical dispersion is a marker of LV mechanical dyssynchrony, however since LV mechanical dispersion has been tested in a broad spectrum of patients who are at increased risk of VA or SCD in contrast to LV mechanical dyssynchrony, this term was used.⁶⁻⁸ This is the first study that associates strain echocardiography parameters with VA and SCD in patients with advanced CKD. However, the relatively small number of patients presenting with events precluded us of performing multivariate analysis to investigate the independent association of advanced echocardiographic parameters and the occurrence of VA and SCD. Larger prospective studies are

needed to investigate the role of strain echocardiography in risk stratification of SCD in patients with advanced CKD.

Limitations

This study has several limitations including its observational, retrospective design. Secondly, some of the echocardiographic measurements for chamber quantification or valve regurgitation were performed following previous recommendations whereas currently recommended 3-dimensional quantification were not systematically available. Furthermore, selection of patients according to the echocardiographic image quality (allowing reliable speckle tracking analysis) and completeness of the echocardiographic examination may introduce a selection bias. The frequency of VA and SCD of 6% in our population may be affected by this selection bias and the retrospective design. In addition, LV GLS may have been influenced by loading conditions, despite the fact that echocardiography was performed after dialysis. Patients with atrial fibrillation were not excluded as long as the beat-to-beat variability allowed reliable analysis of LV GLS and LV mechanical dispersion. The present results cannot be applied to patients with atrial fibrillation and high beat-to-beat variability. In the present study, the LV apex is included in the analysis of LV mechanical dispersion, due to a limitation in the software. Lastly, since this study has a retrospective design it is not possible to make conclusions about predicting future development of VA or SCD.

Conclusion

LV mechanical dispersion along with LV GLS may provide additional valuable risk markers of VA and SCD in pre-dialysis and dialysis patients.

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Chapter 5

VALVULAR HEART DISEASE IN PRE-DIALYSIS AND DIALYSIS PATIENTS: PROGNOSTIC IMPLICATIONS

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ABSTRACT

Aims

Patients with chronic kidney disease (CKD) have an increased risk for valvular heart disease (VHD) due to hemodynamic factors and metabolic pathways that promote valvular calcification and dysfunction. The prevalence of VHD in patients with CKD however, is unclear. The aim of the present study was to investigate the prevalence of VHD and its prognostic implications in pre-dialysis and dialysis patients.

Methods and results

From a retrospective cohort of pre-dialysis and dialysis patients (CKD stage 3b-5) who underwent clinically indicated echocardiography, the presence of significant VHD was assessed. Patients were divided into two groups according to the presence of significant VHD, defined as moderate or severe mitral regurgitation, mitral stenosis, tricuspid regurgitation, aortic regurgitation and/or aortic stenosis. Patients were followed-up for the occurrence of all-cause mortality. Of 281 pre-dialysis and dialysis patients (66% men, mean age 62 ± 14 years), 74 (26%) had significant VHD. During a median follow-up duration of 30 months (IQR; 16, 60 months), 14% of patients with significant VHD underwent surgical or transcatheter valve replacement or repair and 33% of patients died. The cumulative mortality rates at 12, 24 and 36 months were 27%, 40% and 45% for patients with significant VHD versus 8%, 12%, and 18% for patients without significant VHD (log-rank $P < 0.001$).

Conclusion

The prevalence of significant VHD in pre-dialysis and dialysis patients is 26%. Surgical or transcatheter valve replacement or repair was performed infrequently. In this population, patients with significant VHD had significantly increased risk of all-cause mortality compared to patients without significant VHD.

INTRODUCTION

The prevalence of significant (moderate and severe) valvular heart disease (VHD) in the general population of the United States of America is 2.5%.¹ Degenerative etiology is the most frequent cause of VHD and an increase in prevalence of VHD is projected due to the larger life expectancy and ageing process.² Patients with chronic kidney disease (CKD) have an increased risk for developing VHD due to hemodynamic factors and metabolic pathways that promote valvular calcification and valvular dysfunction.^{3,4} However, the prevalence of significant VHD in CKD patients remains unclear.⁵ Surgical or transcatheter valve replacement or repair are the only curative or supportive therapies for VHD. However, patients with advanced CKD are often denied or not referred to surgery due to the increased operative risk.^{6,7} The prognostic implications of untreated severe VHD in the general population are well known, but have not been studied extensively in patients with CKD.⁸ Accordingly, the objectives of the present study were to assess the prevalence of VHD in a well-characterized cohort of pre-dialysis and dialysis patients and its prognostic implications, including frequency of surgical or transcatheter valve intervention and all-cause mortality.

METHODS

Patient population and protocol

Pre-dialysis and dialysis patients from an ongoing registry at the Leiden University Medical Centre were selected for this retrospective study.⁹ Pre-dialysis and dialysis patients who underwent clinically indicated transthoracic echocardiography were included in the present study, introducing a selection bias and potentially underestimating the prevalence of VHD. In patients receiving dialysis, echocardiography was performed after dialysis sessions (meaning dry weight), to avoid volume overload that could increase the frequency of significant valvular heart disease (particularly in terms of valvular regurgitation). Patients were diagnosed with CKD stage 3b-5 according to the 2012 Clinical Practice Guideline for the Evaluation and Management of CKD by Kidney Disease: Improving Global Outcomes.¹⁰ Patients with a history of heart valve replacement or repair, younger than 18 years old and with inadequate echocardiographic image quality for off-line analysis were excluded. Clinical data, including demographics, medication

use, cardiovascular risk factors and laboratory results were collected in the departmental cardiology information system (EPD-vision; Leiden University Medical Centre, Leiden, The Netherlands) and electronic medical records (HiX; ChipSoft, Amsterdam, The Netherlands) and retrospectively analysed. Estimated glomerular filtration rate (eGFR) was calculated by the CKD Epidemiology Collaboration (CKD-EPI) equation.¹⁰ In dialysis patients, residual renal function was calculated by the creatinine clearance using the pre-dialysis plasma creatinine concentration and the concentration of creatinine in a 24-hours urine specimen.¹¹ The occurrence of surgical or transcatheter valve treatment, endocarditis, aortic dissection and renal transplantation during follow-up was registered through case record review. All-cause mortality during follow-up was registered through case record review and the national death registry. The institutional review board approved this retrospective evaluation of clinically acquired data and waved the need for patient written informed consent.

Transthoracic echocardiography

Echocardiographic data were obtained with the patient in the left lateral decubitus position using commercially available systems (Vivid 7 or E9, General Electric Vingmed, Milwaukee, WI, USA) equipped with 3.5 MHz or M5S transducers and digitally stored in cineloop format for off-line analysis (EchoPac 112.0.1, GE Medical Systems, Horten, Norway). On M-mode recordings from the parasternal long-axis view, linear dimensions of the left ventricle were measured and left ventricular (LV) mass index was calculated and indexed to body surface area.¹² LV end-diastolic and end-systolic volumes were measured from the apical 4- and 2-chamber views and LV ejection fraction was calculated using the biplane Simpson's method.¹² Using the disk summation technique, the left atrial (LA) volume was measured in the apical 4-chamber view and indexed to body surface area. In the focused apical 4-chamber view of the right ventricle, the tricuspid annular plane systolic excursion, a measure of right ventricular function, was assessed on anatomical M-mode.¹² LV diastolic parameters consisted of peak early diastolic (E) and late diastolic (A) wave velocities, measured using pulsed wave Doppler recordings of the mitral inflow. Lateral E' mitral annulus velocity was measured with tissue Doppler imaging in the apical 4-chamber view at the lateral side of the mitral annulus and the E/E' ratio was calculated.¹³

The severity of mitral regurgitation (MR) was graded semi-quantitatively by measuring the width of the vena contracta in the parasternal long-axis or apical

4-chamber views.¹⁴ MR was characterized as mild (vena contracta of 0.1-2.9 mm), moderate (vena contracta between 3 and 6.9 mm) or severe (vena contracta ≥ 7 mm).¹⁴ In patients with calcified leaflets, MR was graded quantitatively, the proximal isovelocity surface area (PISA) was used to calculate the effective regurgitant orifice area (EROA) and the regurgitant volume (Rvol). The etiology of MR was defined as primary, when the leaflets of the mitral valve were structurally abnormal, or secondary, when the lack of leaflet coaptation was due to LV dilation and tethering of the leaflets. Mitral stenosis (MS) grade was estimated by measuring the mean gradient and mitral valve area using the pressure half-time method in the apical window.¹⁵ MS was defined as mild (mean gradient < 5 mmHg and valve area > 1.5 cm²), moderate (mean gradient 5-10 mmHg and valve area 1.0-1.5 cm²) or severe (mean gradient > 10 mmHg and valve area < 1.0 cm²).¹⁵ Tricuspid regurgitation (TR) severity was classified qualitatively by the continuous wave signal of the TR jet and semi-quantitatively by measuring the width of the vena contracta in the apical 4-chamber view.¹⁴ TR was defined as mild (faint/parabolic continuous wave signal of TR jet), moderate (dense/parabolic continuous wave signal of TR jet and vena contracta < 7 mm) or severe (dense/triangular with early peaking continuous wave signal of TR jet and vena contracta ≥ 7 mm).¹⁴ Aortic regurgitation (AR) was graded semi-quantitatively by measuring the pressure half-time of the continuous wave spectral signal of AR on the apical 5-chamber view.¹⁴ AR was characterized as mild (pressure half time > 500 ms), moderate (pressure half time of 500-200 ms) or severe (pressure half time < 200 ms).¹⁴ Aortic stenosis (AS) grade was estimated by measuring the aortic valve area, aortic jet velocity and the mean gradient in the parasternal and apical long-axis view or 5-chamber view.¹⁵ AS was defined as mild (aortic valve area > 1.5 cm²), moderate (aortic valve area 1.0-1.5 cm²) or severe (aortic valve area < 1.0 cm²).¹⁵ Patients were divided into two groups according to the existence of one or more significant VHD, defined as moderate or severe MR, MS, TR, AR and/or AS.

Statistical analysis

Continuous data were reported as mean $\pm$ standard deviation and median with interquartile range (IQR), as appropriate. Categorical data were reported as frequencies and percentages. Patients were divided into two groups according to the existence of significant VHD. Differences between the two groups were analysed using the Student's t-test or Mann-Whitney U-test for continuous data

and the chi-square test or Fisher's exact test for categorical data, as appropriate. The Kaplan-Meier method was used to calculate the cumulative event-free survival rates for all-cause mortality from the time of echocardiography. To compare the cumulative event-free survival rates between the two groups, the log-rank test was used. Univariable and multivariable Cox's proportional hazard analysis were performed to determine the independent association between significant VHD and all-cause mortality. All statistical tests were two sided. A P-value <0.05 was considered to indicate significance. Statistical analyses were performed using SPSS software (Version 20.0. Armonk, NY: IBM Corp)

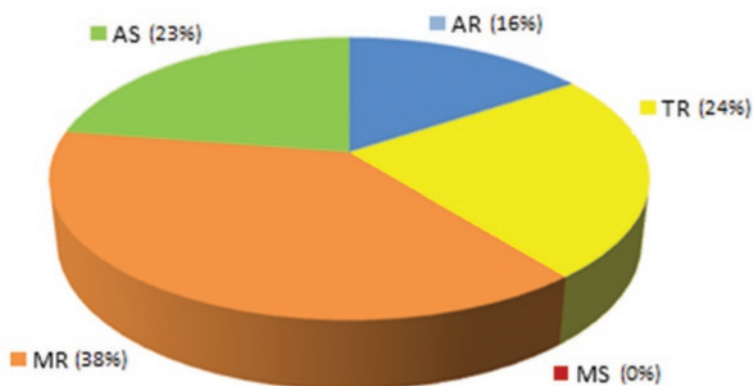


Figure 1. Prevalence of mitral regurgitation (MR), mitral stenosis (MS), tricuspid regurgitation (TR), aortic regurgitation (AR) and aortic stenosis (AS), in pre-dialysis and dialysis patients with significant valvular heart disease.

RESULTS

Patient population

Of 281 pre-dialysis and dialysis patients (66% men, mean age 62 ± 14 years), 74 (26%) patients had one or more significant VHD. More specifically, 39 (38%) patients had significant MR (23 patients with moderate MR, 16 patients with severe MR), 24 (24%) patients had significant TR (18 patients with moderate TR, 6 patients with severe TR), 16 (16%) patients had significant AR (16 patients with moderate AR) and 23 (23%) patients had significant AS (19 patients with moderate AS, 4 patients with severe AS) (Figure 1). There were no patients with

significant MS. Of the 39 patients with significant MR, 24 patients had secondary MR and 15 patients had primary MR (Table 1).

Table 1. Prevalence of significant valvar heart disease in pre-dialysis and dialysis patients

Variable	Frequency	Percent
Aortic stenosis	16	22%
Aortic regurgitation	9	12%
Mitral regurgitation	18	24%
Tricuspid regurgitation	8	11%
Aortic stenosis and aortic regurgitation	2	3%
Aortic stenosis and mitral regurgitation	2	3%
Aortic regurgitation and mitral regurgitation	3	4%
Mitral regurgitation and tricuspid regurgitation	11	15%
Aortic regurgitation, mitral regurgitation and tricuspid regurgitation	2	3%
Aortic stenosis, mitral regurgitation and tricuspid regurgitation	3	4%

Patients with significant VHD were older, received less often kidney transplantation, had a higher heart rate and more frequently presented with NYHA class III-IV heart failure symptoms, peripheral artery disease and atrial fibrillation compared to patients without significant VHD. Furthermore, patients with significant VHD more often used oral anticoagulation and had lower albumin levels compared to patients without significant VHD (Table 2).

Table 3 shows the echocardiographic characteristics of the groups. Patients with significant VHD had larger LV end-diastolic and end-systolic diameters and volumes, lower LV ejection fraction, larger left atrial volume index and higher LV mass index compared to patients without significant VHD. LV filling pressures were higher in patients with versus without significant VHD.

Table 2. Characteristics of pre-dialysis and dialysis patients with and without significant valvular heart disease

Variable	No significant VHD (n=207)	Significant VHD (n=74)	P-value
<u>Clinical characteristics:</u>			
Age (years)	59 ± 14	68 ± 13	<0.001
Men	136 (66%)	49 (66%)	0.936
Dialysis (vs. pre-dialysis)	70 (34%)	29 (39%)	0.406
Dialysis type (HD) ¹	52 (74%)	23 (79%)	0.595
Dialysis vintage (days) ¹	172 (70-385)	121 (40-300)	0.260
Renal transplant	90 (43%)	11 (15%)	<0.001
Heart rate (beats per minute)	71 ± 13	77 ± 20	0.017
Systolic BP (mmHg)	137 ± 20	135 ± 26	0.576
Diastolic BP (mmHg)	78 ± 11	76 ± 15	0.307
Body mass index (kg/m ²)	26 ± 5	25 ± 4	0.231
NYHA class III-IV	6 (3%)	14 (20%)	<0.001
Smoker	119 (60%)	47 (68%)	0.220
Diabetes mellitus	63 (30%)	18 (24%)	0.319
Hypertension	173 (84%)	61 (82%)	0.821
Hypercholesterolemia	83 (40%)	22 (30%)	0.114
Previous MI	45 (22%)	21 (28%)	0.248
Previous CABG/PCI	47 (23%)	18 (24%)	0.777
Peripheral artery disease	26 (13%)	19 (26%)	0.008
Atrial fibrillation	22 (11%)	25 (34%)	<0.001
<u>Medications:</u>			
Diuretics	126 (62%)	50 (70%)	0.223
ACE inhibitor/ARB	129 (64%)	42 (59%)	0.481
B-blocker	114 (56%)	48 (68%)	0.099
Calcium antagonist	90 (45%)	23 (32%)	0.074
Statin	125 (62%)	40 (56%)	0.411
Antiplatelet	71 (35%)	26 (37%)	0.824
Oral anticoagulation	36 (18%)	25 (35%)	0.002
Nitrates	18 (9%)	11 (15%)	0.122

Table 2. Continued

Variable	No significant VHD (n=207)	Significant VHD (n=74)	P-value
<u>Laboratory results:</u>			
RRF (ml/min/1.73m ²) ¹	4.9 (2.1-8.6)	5.3 (2.8-7.7)	0.844
eGFR CKD-EPI (mL/min/1.73m ²) ²	18 ± 7	19 ± 7	0.498
Creatinine (umol/L) ²	327 ± 122	302 ± 110	0.227
Urea (mmol/L)	22 ± 7	23 ± 8	0.340
Corrected calcium (mmol/L)	2.2 ± 0.1	2.2 ± 0.1	0.692
Phosphate (mmol/L)	1.4 ± 0.4	1.4 ± 0.4	0.759
Parathyroid hormone (pmol/L)	15 (7-25)	16 (10-28)	0.189
Albumin (g/L)	42 ± 5	39 ± 6	0.001
Glucose (mmol/L)	6 ± 3	6 ± 2	0.749
LDL-cholesterol (mmol/L)	2.4 ± 1.2	2.4 ± 1.1	0.956
Hemoglobin (mmol/L)	7.3 ± 1.0	7.1 ± 1.0	0.260

¹Measured only in dialysis patients.²Measured only in pre-dialysis patients.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; CABG, coronary artery bypass graft; CKD-EPI, chronic kidney disease epidemiology collaboration; eGFR, estimated glomerular filtration rate; HD, hemodialysis; LDL, low-density lipoprotein; MI, myocardial infarction; NTX, renal transplantation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RRF, residual renal function; VHD, valvular heart disease.

Continuous data are presented as mean ± SD or median (interquartile range). Categorical data are presented as numbers and percentages.

Table 3. Echocardiographic characteristics of pre-dialysis and dialysis patients with and without significant valvular heart disease

Variable	No significant VHD (n=207)	Significant VHD (n=74)	P-value
IVSTd (mm)	11 ± 2	11 ± 3	0.053
PWTd (mm)	10 ± 2	10 ± 2	0.694
LVEDD (mm)	51 ± 8	55 ± 11	0.003
LV mass index (gm/m ²)	108 ± 35	130 ± 37	<0.001
LVESD (mm)	33 ± 9	40 ± 13	<0.001
LVEDV (ml)	102 ± 39	138 ± 74	<0.001
LVESV (ml)	42 ± 26	78 ± 68	<0.001
LVEF (%)	60 ± 13	49 ± 18	<0.001
LAVI (mL/m ²)	25 ± 12	35 ± 16	<0.001
TAPSE (mm)	18 ± 4	17 ± 5	0.174
Peak E-wave velocity (cm/s)	70 ± 23	82 ± 32	0.006
Peak A-wave velocity (cm/s)	80 ± 24	80 ± 29	0.981
Lateral E' (cm/s)	6 ± 3	5 ± 3	0.023
Lateral E/E'	11 (8-16)	16 (10-23)	0.001

IVSTd, interventricular septum thickness in diastole; LAVI, left atrial volume index; LV, left ventricular; LVEDD, left ventricular end diastolic diameter; LVEDV, left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVESV, left ventricular end systolic volume; PWTd, posterior wall thickness in diastole; TAPSE, tricuspid annular plane systolic excursion; VHD, valvular heart disease. Continuous data are presented as mean ± SD or median (interquartile range). Categorical data are presented as numbers and percentages.

Follow-up

During a median follow-up duration of 30 months (IQR; 16, 60 months), 14% of patients with significant VHD underwent surgical or transcatheter valve replacement or repair. More specifically, 4 patients underwent surgical valve replacement or repair (2 patients underwent aortic valve replacement, 1 patient underwent aortic and mitral valve replacement and 1 patient underwent mitral and tricuspid valve repair), 6 patients underwent transcatheter valve replacement or repair (4 patients underwent mitralclip, 1 patient underwent transfemoral transcatheter aortic valve implantation (TAVI) and 1 patient underwent balloon dilatation of the aortic valve), and 1 patient presented with endocarditis. There

were no patients presenting with aortic dissection during follow-up. Thirty-six percent of patients received renal transplantation and 33% of patients died. Figure 2 shows the Kaplan-Meier curves of the cumulative event-free survival for all-cause mortality in patients with and without significant VHD. The cumulative mortality rates at 12, 24 and 36 months were 27%, 40% and 45% for patients with significant VHD versus 8%, 12%, and 18% for patients without (log-rank $P<0.001$).

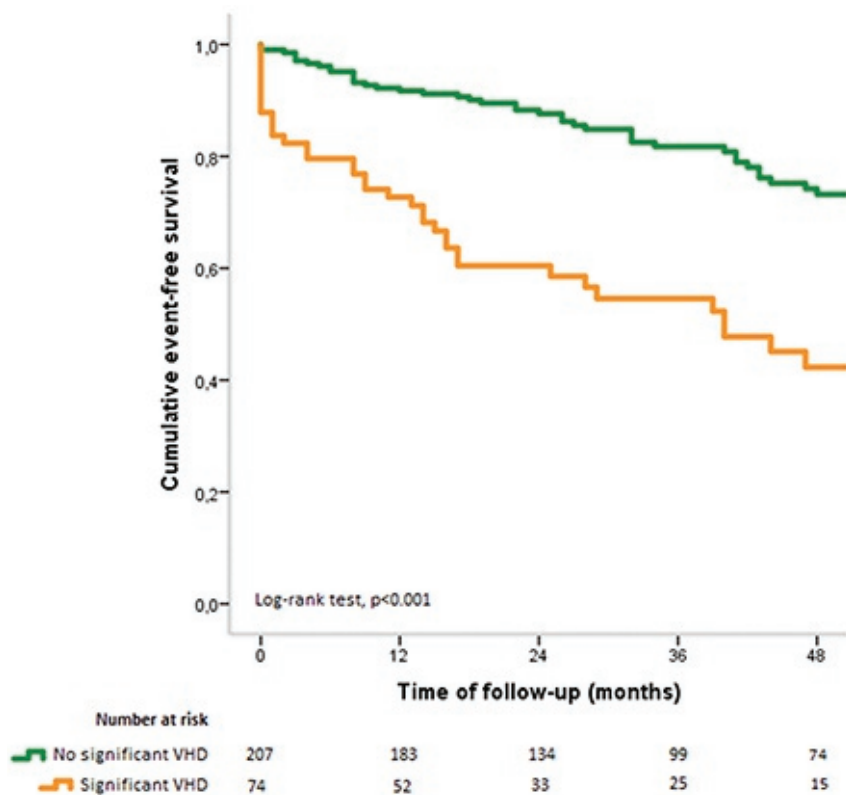


Figure 2. Kaplan-Meier curves demonstrating the relationship between significant valvular heart disease (VHD) and all-cause mortality in pre-dialysis and dialysis patients.

On univariable analyses age, renal transplantation, heart rate, NYHA class III-IV, peripheral artery disease, atrial fibrillation, albumin levels, LV mass index, LV ejection fraction, LA volume index, lateral E/E' and significant VHD were associated with all-cause mortality (Table 4). On multivariable analysis, significant VHD was independently associated with increased risk of all-cause mortality

after correcting for age, renal transplantation, NYHA class III-IV, LV mass index, LV ejection fraction, LA volume index and lateral E/E' (Table 4).

Table 4. Cox proportional hazard model showing the association between clinical and echocardiographic variables and the endpoint of all-cause mortality in pre-dialysis and dialysis patients with significant valvar heart disease

	Univariable HR (95% CI)	P-value	Multivariable HR (95% CI)	P-value
Age	1.07 (1.05-1.09)	<0.001	1.04 (1.02-1.06)	<0.001
Male gender	1.22 (0.78-1.90)	0.384		
RTx future	0.12 (0.06-0.26)	<0.001	0.23 (0.098-0.53)	0.001
Heart rate (bpm)	1.02 (1.01-1.03)	0.006		
NYHA class III-IV	3.38 (1.90-5.99)	<0.001	1.72 (0.76-3.87)	0.192
Peripheral artery disease	3.21 (2.03-5.07)	<0.001		
Atrial fibrillation	2.16 (1.35-3.47)	0.001		
Oral anticoagulation	1.58 (0.99-2.53)	0.056		
Albumin	0.89 (0.86-0.92)	<0.001		
LV mass index (gm/m ²)	1.01 (1.00-1.01)	0.046	0.995 (0.98-1.01)	0.213
LVEF (%)	0.97 (0.96-0.99)	<0.001	0.99 (0.98-1.01)	0.436
LAVI (mL/m ²)	0.98 (0.95-1.01)	0.027	1.01 (0.99-1.03)	0.370
Lateral E/E'	1.01 (1.00-1.02)	0.005	1.01 (0.99-1.03)	0.236
Significant VHD	3.09 (2.05-4.68)	<0.001	1.90 (1.12-3.22)	0.017

BPM, beats per minute; CI, confidence interval; LAVI, left atrial volume index; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association classification; OR, odds ratio; RTx, renal transplantation; VHD, valvular heart disease.

DISCUSSION

In the present study, the prevalence of significant VHD among pre-dialysis and dialysis patients is as high as 26%. However, only 14% of the patients with significant VHD were referred for surgical or transcatheter valve replacement or repair. The presence of VHD was associated with poor survival in this population.

Prevalence of significant VHD in patients with CKD

Data on the prevalence of significant VHD in patients with CKD are limited.⁵ In 62 patients with end-stage renal disease on long-term hemodialysis, mild

to severe VHD was observed in 18 (29%) patients.⁵ In contrast, in the general population the age-adjusted prevalence of moderate to severe VHD was 2.5% (95% confidence interval: 2.2%-2.7%).¹ The higher prevalence of VHD in patients with CKD compared to the general population is caused by increased valvular calcification, cardiac dilatation and infective endocarditis.^{3,16-18} Advanced CKD is associated with chronic volume overload leading to hypertension, increased cardiac output and peak flow velocity which generate flow turbulence.³ Increased flow turbulence causes mechanical stress on the valves, which leads to valvular calcification and fibrosis.³ In addition, chronic pressure overload, inflammation and dysregulated metabolic pathways, such as disorders in the calcium-phosphate metabolism, may lead to valvular calcification and secondary valvular dysfunction.^{3,17,19} Cardiac dilatation, as a result of chronic volume overload, also causes valvular dysfunction by preventing appropriate coaptation of the leaflets.¹⁶ The dynamic nature of valve regurgitation is well known and after intensified ultrafiltration, functional mitral and tricuspid regurgitation can disappear.¹⁶ This highlights the difficulty in estimating the true prevalence of functional mitral and tricuspid regurgitation since their presence will depend on the loading conditions of the patient. In addition, hemodialysis patients have an increased risk for infective endocarditis.¹⁸ In 9,393 patients undergoing hemodialysis, infective endocarditis was diagnosed in 150 patients, compared to 250 patients of 17,6369 age- and gender matched controls, yielding a 38-fold increased risk of endocarditis in hemodialysis patients.¹⁸

Treatment of patients with CKD and significant VHD

Fourteen percent of pre-dialysis and dialysis patients with significant VHD in our cohort underwent surgical or transcatheter valve replacement or repair during a median follow-up of 30 months (IQR; 16, 60 months). The therapeutic management of patients with CKD and significant VHD has not been extensively studied.²⁰ In a 5-year multicentre French survey conducted between 1988 and 1992, 98 chronic dialysis patients with severe VHD were identified and 62% of these patients underwent surgical valve replacement or repair.²⁰ The Euro Heart Survey on VHD conducted in 2001 identified 3,596 patients with mild to severe native valve disease and 31% of these patients underwent surgical valve replacement or repair during the survey period of 30 days.⁶ Patients with CKD and severe VHD are often denied or not referred to heart valve replacement or repair, because of the high risk for surgery.^{6,7} In high risk and inoperable

patients, transcatheter valve replacement or repair has emerged as a promising therapeutic intervention for severe VHD.^{21,22} However, patients with severe renal insufficiency were excluded from these trials.^{21,22} Data from the German registry on aortic stenosis, including 28,716 patients, showed a prevalence of CKD (stage 1-5) of 39%.²³ Seventy percent of these patients received a transfemoral TAVI and 30% a transapical TAVI. The in-hospital mortality rates of patients with stage 5 CKD was significantly higher as compared to patients with normal renal function (9.6% for transfemoral TAVI and 17.5% for transapical TAVI vs. 5.2% and 8.2%, respectively).²³ Interestingly, the in-hospital mortality for transfemoral TAVI is lower to that of dialysis patients undergoing cardiac operations (15.3%).²⁴ Therefore, transcatheter valve replacement or repair could be a promising therapy for patients with CKD and severe VHD.

Prognostic implications of significant VHD in patients with CKD

Pre-dialysis and dialysis patients with significant VHD had significantly increased risk of all-cause mortality compared to patients without significant VHD. Only 14% of patients with significant VHD in the present study were treated with surgical or transcatheter valve replacement or repair. Patients with CKD have an increased risk for all-cause mortality and CKD patients with significant VHD have an even higher risk, partly due to the low percentage of surgical or transcatheter valve replacement or repair in these patients. The high mortality risk in patients with CKD and significant VHD indicates the importance of appropriate treatment of these patients. Prospective studies are needed to investigate the role of transcatheter valve replacement and repair in patients with CKD and severe VHD.

Limitations

Several limitations should be acknowledged. The present study is an observational retrospective study, single-center, with relatively small number of patients and the study population was heterogeneous with different valve pathologies. Furthermore, only pre-dialysis and dialysis patients who underwent clinically indicated transthoracic echocardiography were included in the present study, introducing a selection bias and potentially underestimating the prevalence of VHD. In addition, echocardiography was performed after the dialysis sessions, where the severity of VHD may have been changed by loading conditions. Unfortunately, there were not enough patients to compare the survival of patients treated with surgical or with transcatheter valve replacement or repair.

Conclusion

The prevalence of significant VHD in pre-dialysis and dialysis patients is 26% and 14% of these patients underwent surgical or transcatheter valve replacement or repair. Patients with significant VHD had significantly increased risk of all-cause mortality compared to patients without significant VHD. Significant VHD was independently associated with an increased risk of all-cause mortality.

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Chapter 6

PREVALENCE AND PROGNOSTIC IMPLICATIONS OF MITRAL AND AORTIC VALVE CALCIUM IN PATIENTS WITH CHRONIC KIDNEY DISEASE

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ABSTRACT

Valvular calcium can be observed in patients with severe chronic kidney disease (CKD). However, the prevalence and prognostic implications of left-sided valve calcium in patients with stage 2 and 3 CKD (estimated glomerular filtration rate (eGFR) of 60-89 and 30-59 mL/min/1.73m² respectively) is unknown. The present study investigates the prevalence of mitral and aortic valve calcium in patients with stage 2 and 3 CKD and to evaluate its association with all-cause mortality. In patients with stage 2 and 3 CKD who underwent clinically indicated coronary computed tomography angiography (CTA), the presence of mitral and/or aortic valve calcium was assessed. Patients were divided into 2 groups according to the presence of mitral and/or aortic valve calcium on coronary CTA. Patients were followed for the occurrence of all-cause mortality (primary endpoint). Of 204 stage 2 and 3 CKD patients (54% men, mean age 60±10 years), 66 (32%) patients had mitral and/or aortic valve calcium. During a median follow-up of 6 years (IQR; 2, 9 years), 29 (14%) patients died. Patients with mitral and/or aortic valve calcium showed significantly higher mortality rates compared to patients without left-sided valve calcium (Log-rank P=0.009). Mitral valve calcium was independently associated with increased risk of all-cause mortality, whereas aortic valve calcium was not. In conclusion, the prevalence of left-sided valve calcium in patients with stage 2 and 3 CKD is high. Mitral valve calcium was independently associated with increased risk of all-cause mortality, whereas aortic valve calcium was not.

INTRODUCTION

Patients with chronic kidney disease (CKD) exhibit an increased risk of cardiovascular morbidity and mortality.¹ Valvular heart disease is one of the contributors to these increased morbidity and mortality risks.² In CKD patients, valvular calcium is an important underlying mechanism of valve dysfunction.³ Hypertension, inflammation and dysregulated metabolic pathways, such as disorders in the calcium-phosphate metabolism, lead to the development of valvular calcium in patients with CKD.^{4,5} Valvular calcium is associated with an increased risk of all-cause mortality in patients with end-stage renal disease.^{6,7} However, the prognostic implications of left-sided valve calcium in patients with stage 2 and 3 CKD (eGFR of 60-89 mL/min/1.73m² and 30-59 mL/min/1.73m² respectively) are unknown. Therefore the aim of the present study was to investigate the prevalence of mitral and aortic valve calcium in patients with stage 2 and 3 CKD using coronary computed tomography angiography (CTA) and to evaluate its association with all-cause mortality.

METHODS

Coronary CTA data clinically acquired in patients with stage 2 and 3 CKD between 2005 and 2011 at the Leiden University Medical Centre were retrospectively analysed. Patients were diagnosed with stage 2 and 3 CKD according to the 2012 Clinical Practice Guideline for the evaluation and Management of CKD, Kidney Disease: Improving Global Outcomes (KDIGO).⁸ Patients who underwent coronary CTA for screening of transcatheter aortic valve implantation, who underwent mitral and/or aortic valve replacement or repair before index coronary CTA, who were younger than 18 years old and patients with complex congenital heart disease were excluded. The clinical indications for coronary CTA were: screening for coronary artery disease, chest pain, pulmonary vein antrum isolation (PVAI) and ventricular tachycardia ablation. Clinical data were collected through review of the electronic medical records (HiX; ChipSoft, Amsterdam, The Netherlands) and the departmental cardiology information system (EPD-vision; Leiden University Medical Centre, Leiden, The Netherlands) and retrospectively analysed. eGFR was calculated by the Modified Diet in Renal Disease equation.⁹ Patients were followed for the occurrence of all-cause mortality through case record review and the national death registry.

The occurrence of surgical or transcatheter mitral or aortic valve replacement or repair during follow-up was registered through case record review. For retrospective analysis of clinically acquired data, anonymously handled, the institutional review board approved the study and waived the need for patient written informed consent.

Patients were scanned using a 64-slice multidetector row computed tomography (CT) scanner (Aquilion 64, Toshiba Medical Systems, Japan) or a 320-slice CT scanner (Toshiba Multi-slice Aquilion ONE system, Toshiba Medical Systems, Japan). Heart rate and blood pressure were monitored before coronary CTA data acquisition. Patients with a heart rate exceeding 60 beats per minute received metoprolol orally or intravenously. If tolerated, sublingual nitroglycerin was administered to induce coronary artery vasodilation. A non-contrast CT scan was performed for coronary artery calcification burden quantification, followed by contrast coronary CTA for evaluation of obstructive coronary artery disease (CAD). All scan parameters have been previously described.¹⁰ Commercially available, post-processing software was used for data analysis (Vitrea FX 6.5; Vital Images, Minnetonka, Minnesota, USA). Calcium burden of the mitral and aortic valve was quantified using the Agatston algorithm as previously published.^{11,12} Coronary anatomy was assessed systematically according to a 17-segment coronary tree model.¹³ Obstructive CAD was defined as $\geq 50\%$ stenosis in a coronary artery. Patients were divided into two groups according to the existence of mitral and/or aortic valve calcium. Examples of patients at different CKD stages with or without mitral or aortic valve calcium are demonstrated in Figures 1 and 2.

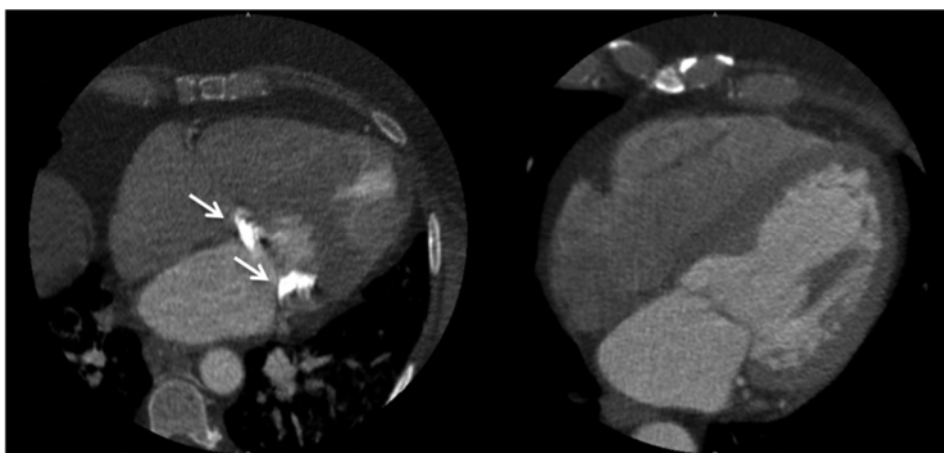


Figure 1. Coronary computed tomography angiography images in a patient with stage 3 chronic kidney disease and significant mitral valve calcium (left panel, arrows) and in a patient with stage 2 chronic kidney disease and no mitral valve calcium (right panel).

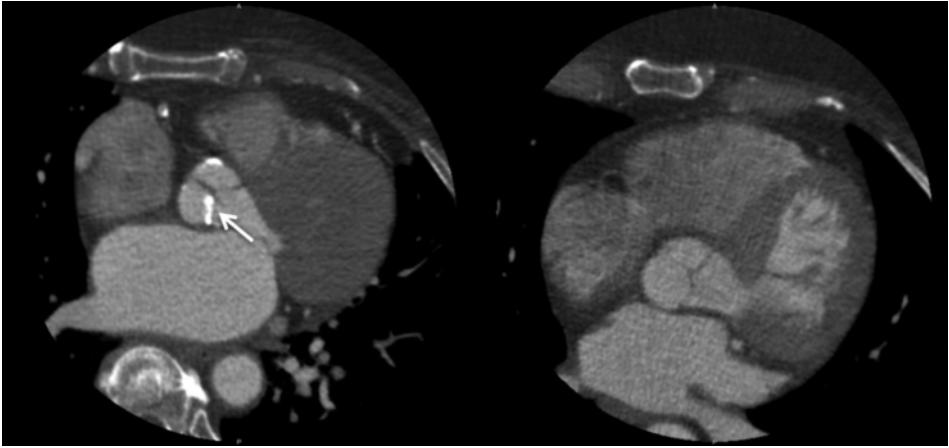


Figure 2. Coronary computed tomography angiography images in a patient with stage 3 chronic kidney disease and significant aortic valve calcium (left panel, arrow) and in a patient with stage 2 chronic kidney disease and no aortic valve calcium (right panel).

Continuous variables are reported as median and interquartile range or mean $\pm$ standard deviation, as appropriate. Categorical variables are reported as numbers and percentages. Continuous variables were compared between the groups using the Student's T-test or Mann-Whitney U-test, as appropriate. Categorical variables were compared between the groups using the chi-square test. The Kaplan-Meier method was used to calculate the cumulative event-free survival rates for all-cause mortality from the time of coronary CTA acquisition. The log-rank test was used to compare the cumulative event-free survival rates between groups. Univariable and multivariable Cox proportional hazard models were used to evaluate the independent association between mitral or aortic valve calcium with all-cause mortality. The occurrence of surgical or transcatheter mitral or aortic valve replacement or repair during follow-up was introduced as a time-dependent covariate. All analyses were performed with the use of the SPSS software (Version 20.0. Armonk, NY: IBM Corp). A two-sided P-value < 0.05 was considered statistically significant.

RESULTS

Of 204 stage 2 and 3 CKD patients (54% men, mean age 60 ± 10 years), 66 (32%) patients had mitral and/or aortic valve calcium. More specifically, 15 (23%) patients had both mitral and aortic valve calcium, 42 (64%) patients had only

aortic valve calcium and 9 (14%) patients had only mitral valve calcium. Patients with mitral and/or aortic valve calcium were older, had higher body mass index and more obstructive CAD on coronary CTA compared to patients without left-sided valve calcium (Table 1). CKD stage was not significantly different between patients with or without aortic valve calcium; however in patients with mitral valve calcium, stage 3 CKD was more frequent compared to patients without mitral valve calcium (15 patients (63%) versus 65 patients (36%) respectively, $P=0.013$). Ten patients had at baseline significant left-sided valvular heart disease.

Table 1. Baseline characteristics of chronic kidney disease patients with and without mitral and/or aortic valve calcium

Variable	Mitral and/or aortic valve calcium		P value
	No (n=138)	Yes (n=66)	
Age (years)	58 ± 10	65 ± 8	<0.001
Men	73 (53%)	37 (56%)	0.672
Stage 3 CKD	51 (37%)	29 (44%)	0.339
eGFR MDRD (mL/min/1.73m ²)	70 (58-80)	61 (53-79)	0.148
Body mass index (kg/m ²)	27 ± 5	29 ± 6	0.035
Smoker	15 (11%)	9 (14%)	0.566
Diabetes mellitus	35 (25%)	22 (33%)	0.235
Hypertension*	78 (57%)	41 (62%)	0.448
Hypercholesterolemia†	51 (37%)	26 (39%)	0.737
Peripheral artery disease	4 (3%)	3 (5%)	0.552
Previous myocardial infarction	13 (9%)	9 (14%)	0.364
Previous CABG/PCI	14 (10%)	10 (15%)	0.299
Previous stroke	5 (4%)	1 (2%)	0.400
Atrial fibrillation	42 (31%)	22 (33%)	0.725
Coronary artery disease			0.044
None	15 (11%)	4 (6%)	
Non-obstructive	74 (55%)	28 (42%)	
Obstructive	45 (34%)	34 (52%)	

CABG, coronary artery bypass grafting; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; PCI, percutaneous coronary intervention. *Defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg and/or the use of antihypertensive medication. † Defined as serum total cholesterol ≥230 mg/dl and/or serum triglycerides ≥200 mg/dl and/or treatment with lipid lowering drugs. Continuous data are presented as mean ± SD or median (interquartile range). Categorical data are presented as numbers and percentages.

A total of 13 patients underwent surgical or transcatheter mitral or aortic valve replacement or repair after the index coronary CTA. During a median follow-up of 6 years (IQR; 2, 9 years), 29 (14%) patients died. The total follow-up time was 12 years. The Kaplan-Meier survival curves for patients with and without mitral and/or aortic valve calcium are presented in Figure 3. At univariable analysis, age, CKD stage, body mass index, atrial fibrillation, previous myocardial infarction and mitral and aortic valve calcium were associated with all-cause mortality (Table 2). At multivariable analysis, mitral valve calcium was independently associated with increased risk of all-cause mortality after correcting for age, gender, CKD stage, previous myocardial infarction, atrial fibrillation and surgical or transcatheter valve replacement or repair, whereas aortic valve calcium was not (Table 3).

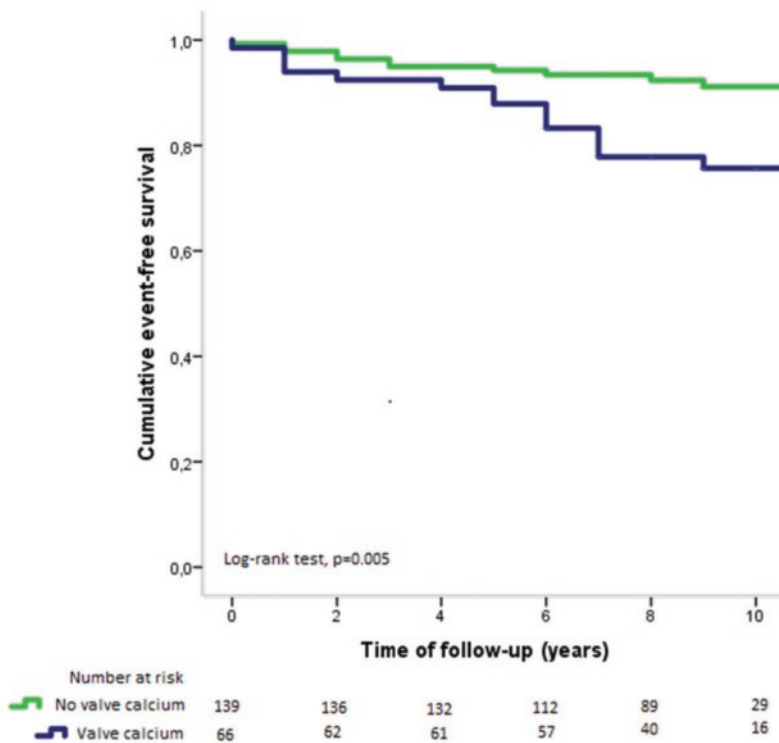


Figure 3. Kaplan-Meier curves with the cumulative event-free survival of stage 2 and 3 chronic kidney disease patients with mitral and/or aortic valve calcium (blue) and patients without (green).

DISCUSSION

In the present study, one-third of patients with stage 2 and 3 CKD had mitral and/or aortic valve calcium. The presence of mitral and/or aortic valve calcium was associated with poor survival in this population, but only mitral valve calcium was independently associated with increased risk of all-cause mortality, whereas aortic valve calcium was not.

Table 2. Univariate cox proportional hazard model demonstrating the association between clinical and computed tomography scan variables and all-cause mortality

Variable	Univariate OR (95% CI)	P value
Age	1.07 (1.03-1.11)	0.001
Male gender	2.00 (0.93-4.31)	0.077
Stage 3 CKD (vs. stage 2 CKD)	2.64 (1.23-5.70)	0.013
Coronary artery disease (versus normal)		
Non-obstructive	0.55 (0.15-1.98)	0.356
Obstructive	0.997 (0.29-3.43)	0.997
Body mass index (kg/m ²)	1.08 (1.02-1.14)	0.009
Atrial fibrillation	2.37 (1.12-5.05)	0.025
Peripheral artery disease	8.29 (2.77-24.79)	<0.001
Previous myocardial infarction	3.91 (1.73-8.85)	0.001
Previous stroke	1.13 (0.15-8.31)	0.905
Surgical or transcatheter valve replacement or repair	6.10 (0.81-45.82)	0.079
Mitral valve calcium	2.93 (1.33-6.46)	0.008
Aortic valve calcium	2.18 (1.05-4.52)	0.036

CAD, coronary artery disease; CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio.

The prevalence of valve calcium is high in patients with end-stage renal disease.^{6,7,14} However the prevalence of left-sided valve calcium in patients with milder CKD is less well established.¹⁵⁻¹⁷ Among 262 patients with CKD (defined as eGFR <60 mL/min/1.73m²) 22% had mitral and/or aortic valve calcium.¹⁶ In addition, in 710 patients with CKD stage 3A (eGFR 45-60 mL/min/1.73m²), 80% had one or more left-sided valves with calcium, whereas in 214 patients with

CKD stage 3B-5 (eGFR <45 mL/min/1.73m²), 88% had one or more left-sided valves with calcium.¹⁵ The different imaging techniques to analyze left-sided valve calcium (coronary CTA vs. echocardiography) and differences in patient characteristics (from age, ethnicity and CKD stage differences, to differences in risk factors) in the abovementioned studies have contributed to the differences in the reported prevalence. Several risk factors for valvular calcium have been proposed in patients with CKD.^{4,18} Among 2070 patients with stage 2 and 3 CKD, 16% had mitral annular calcification.⁴ Age, Caucasian race, decreased GFR and elevated phosphate were independently associated with the presence of mitral annular calcification.⁴ Elevated phosphate stimulates secondary hyperparathyroidism and is associated with increased circulating calcium and increased risk of valvular calcium.^{4,18} In 92 chronic hemodialysis patients, hypertension, age and calcium phosphate product were associated with mitral and/or aortic valve calcium.⁵

Table 3. Multivariable Cox proportional hazard model evaluating the association between mitral and aortic valve calcium and all-cause mortality

	Mitral valve calcium OR (95% CI)	P value	Aortic valve calcium OR (95% CI)	P value
Not adjusted	2.93 (1.33-6.46)	0.008	2.18 (1.05-4.52)	0.036
Adjusted for age	2.32 (1.04-5.14)	0.039	1.55 (0.74-3.27)	0.245
Adjusted for age, gender and CKD stage	2.45 (1.06-5.64)	0.035	1.53 (0.73-3.24)	0.263
Adjusted for multiple factors*	2.65 (1.15-6.13)	0.022	0.74 (0.34-1.59)	0.437

* Adjusted for age, gender, chronic kidney disease stage, previous myocardial infarction, atrial fibrillation, surgical or transcatheter valve replacement or repair.
CI, confidence interval; CKD, chronic kidney disease; OR, odds ratio.

In the current study, mitral valve calcium was associated with worse CKD stage, whereas aortic valve calcium was not. Asselbergs et al. and Fox et al. reported similar findings and suggested that disorders in the calcium-phosphate metabolism may cause mitral valve calcium, while aortic valve calcium may be more a degenerative disease.^{15,16} In a recent series of 23,088 patients with CKD (eGFR <60 mL/min/1.73m²), left-sided valvular heart disease (mitral regurgitation and aortic stenosis) was independently associated with CKD.² Furthermore the

prevalence of at least mild mitral regurgitation was much higher than aortic stenosis (42.9% versus 9.5% respectively), probably indicating the high burden of CKD on the structural changes in the mitral valve apparatus.²

In the current study including patients with stage 2 and 3 CKD, the presence of left-sided valve calcium was associated with higher mortality rates compared to patients without left-sided valve calcium. Furthermore mitral valve calcium was independently associated with an increased risk of all-cause mortality, whereas aortic valve calcium was not. Studies evaluating the prognosis of patients with CKD and left-sided valve calcium are limited.^{6,16} In 262 patients with CKD (defined as eGFR <60 mL/min/1.73m²), mitral annular calcification was associated with a 3-fold increased risk for death.¹⁶ In addition, in 144 hemodialysis patients mitral and aortic valve calcium was associated with higher mortality rates.⁶ However, after adjustment for multiple factors (age, gender, race, diabetes mellitus, atherosclerotic cardiovascular disease and pulse pressure) mitral valve calcium remained associated with all-cause mortality, whereas aortic valve calcium was not.⁶ The reasons for this finding may lay on the type of valve dysfunction that the valvular calcium cause. Aortic valve calcium leads more frequently to aortic stenosis, whereas mitral valve calcium may lead to mitral regurgitation. Symptoms caused by severe aortic stenosis can only be relieved by aortic valve replacement whereas in symptomatic severe mitral regurgitation, the use of diuretics may lead to symptom relief and mitral valve intervention may be deferred in patients with CKD. In addition, the diagnosis of severe mitral regurgitation may be challenged by the loading conditions of the patient and the presence of valvular calcium. Accordingly, patients may not be referred for mitral valve intervention and the risk of all-cause mortality may increase. The high mortality risk in patients with CKD and left-sided valve calcium underscores the importance of appropriate treatment of these patients. Future studies are needed to investigate the association between mitral valve calcium and CKD and subsequently potential therapeutic targets to prevent valvular calcium.

The present study has several limitations, including its retrospective design. In addition, only patients with stage 2 and 3 CKD with a clinically indicated coronary CTA were included in the present study, giving a potential selection bias. Furthermore, low eGFR is associated with severe coronary calcification, which may cause blooming artifacts affecting the interpretation of CTA coronary stenosis severity.

The prevalence of left-sided valve calcium in patients with stage 2 and 3 CKD is high and was associated with poor survival. Mitral valve calcium was independently associated with increased risk of all-cause mortality, whereas aortic valve calcium was not.

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Chapter 7

ECHOCARDIOGRAPHIC ASSOCIATES OF ATRIAL FIBRILLATION IN END-STAGE RENAL DISEASE

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ABSTRACT

Background

The prevalence of atrial fibrillation (AF) in end-stage renal disease (ESRD) patients is relatively high. The present study evaluated the association between left atrial (LA) remodeling, including an increased size and myocardial fibrosis, with slow LA conduction and the occurrence of AF.

Methods

In 171 ESRD patients enrolled in the Implantable Cardioverter Defibrillators in Dialysis patients (ICD2) trial, the LA dimensions, LA conduction delay (as reflected by the time difference between P-wave onset on surface electrocardiogram and A'-wave on tissue Doppler imaging [PA-TDI]) and LA function were compared between patients who exhibited AF versus patients without AF. Based on ICD remote monitoring or clinical records, the occurrence of AF was detected.

Results

Of 171 patients, 47 (27%) patients experienced AF. Despite comparable left ventricular ejection fraction and prevalence of significant mitral regurgitation, patients with AF had significantly larger LA volume index (29 ± 11 vs. 23 ± 10 mL/m², $p=0.001$), longer PA-TDI duration (144 ± 30 vs. 131 ± 27 ms, $p=0.010$) and reduced late diastolic mitral annular velocity (A') (7.1 ± 2.8 vs. 8.2 ± 2.4 cm/s, $p=0.012$) compared to patients without AF. On multivariable analysis, larger LA volume index (odds ratio [OR] 1.04, 95% confidence interval [CI] 1.01-1.08, $p=0.017$), longer PA-TDI duration (OR 1.02, 95% CI 1.00-1.03, $p=0.025$) and reduced A' (OR 0.84, 95% CI 0.72-0.98, $p=0.025$) were independently associated with AF after adjusting for age and LV diastolic relaxation.

Conclusion

ESRD patients with AF show more advanced changes in the LA substrate than ESRD patients without AF.

INTRODUCTION

Atrial fibrillation (AF) is very common in end-stage renal disease (ESRD) patients and the incidence of newly diagnosed AF in older patients initiating dialysis is 5-fold higher than in the general population.¹⁻³ Electrical and structural remodeling of the atrial myocardium serves as a substrate for AF.⁴ In patients with ESRD, the metabolic and hemodynamic disturbances associated with dialysis may modulate the AF substrate contributing to the high incidence of AF.⁵ However, the structural remodeling of the left atrium (LA) has not been characterized in this group of patients. Increased interstitial fibrosis that leads to slow conduction of the activation potential in the LA is one of the structural changes. PA-TDI duration, a parameter derived from echocardiography using tissue Doppler imaging (TDI), measures the delay between electrical conduction and mechanical activation of the LA myocardium and reflects the total atrial conduction time.⁶ It is suggested that a longer PA-TDI duration reflects a higher burden of LA fibrosis.⁷ The present study compares the LA substrate of patients with ESRD with and without AF.

METHODS

Patient population and protocol

The Implantable Cardioverter Defibrillators in Dialysis patients (ICD2) trial (ISRCTN20479861) is an ongoing prospective randomised controlled study evaluating the efficacy and safety of prophylactic ICD therapy in reducing sudden cardiac death rates in patients with ESRD treated with dialysis.⁸ The study protocol has been described previously.⁸ In brief, the inclusion criteria were: ESRD patients in dialysis at least 90 days prior to inclusion, age between 55 and 80 years old. ESRD patients who fulfil current criteria for ICD implantation for primary or secondary prevention and with an expected survival of less than 1 year were not considered for inclusion. Eligible patients were randomised, in a 1:1 fashion to receive an ICD or conventional therapy alone. All patients provided informed consent and the trial design was approved by the local ethics committee.⁸ Baseline evaluations included a 12-lead electrocardiogram (ECG) and transthoracic echocardiogram. In this substudy, patients who were in sinus rhythm at the time of the 12-lead ECG and transthoracic echocardiography were

included. Patients were divided into two groups according to the presence of AF (prior to, or after inclusion in the study). The echocardiographic associates of AF were investigated.

Clinical and electrocardiographic variables

Baseline clinical variables included demographics, cardiovascular risk factors, medication use and laboratory results. Residual renal function was calculated as the mean of creatinine and urea clearance adjusted for body surface area (ml/min per 1.73m²). The mean of post- and pre-dialysis samples (if available) were used to estimate mean plasma creatinine and urea concentrations.⁹ Baseline ECG variables included heart rate, P-wave duration, PR interval, QRS duration, QT interval and corrected QT interval calculated by Bazett's formula (corrected QT = QT/ $\sqrt{\text{RR interval}}$).¹⁰

Echocardiography

Patients were imaged in the left lateral decubitus position using commercially available systems (Vivid 7 or E9, General Electric Vingmed, Milwaukee, WI, USA). Standard 2-dimensional images were acquired using 3.5 MHz or M5S transducers adjusting depth and gain settings. Image acquisition was ECG-triggered and stored in cineloop format for off-line analysis (EchoPac 112.0.1, GE Medical Systems, Horten, Norway). Linear dimensions of the left ventricle (LV) were measured from the parasternal long-axis view using M-mode.¹¹ LV end-diastolic and end-systolic volumes were measured on the apical 4- and 2-chamber views using the biplane Simpson's method and LV ejection fraction was derived.¹¹ LA volume was measured in the apical 4-chamber view using the disk summation technique and was indexed for body surface area. Tricuspid annular plane systolic excursion was measured in the focused apical 4-chamber view of the right ventricle applying anatomical M-mode to assess the right ventricular longitudinal function.¹¹ Mitral regurgitation severity was graded semi-quantitatively from colour-flow Doppler data by measuring the width of the vena contracta.¹² LV diastolic function was assessed by integrating the pulsed wave Doppler data of the mitral valve inflow, TDI data and LA volume.¹³ Peak E (early diastolic) and A (late diastolic) wave velocities were measured on pulsed wave Doppler recordings of the mitral inflow. Lateral E' and A' were measured using color-coded TDI at the lateral side of the mitral annulus in the apical 4-chamber view.¹³ Tricuspid regurgitation gradient was measured on continuous wave

Doppler tracings of the tricuspid valve. Pulmonary pressures were estimated by adding to the transtricuspid regurgitant gradient 5-15 mmHg depending on collapsibility of the inferior vena cava as previously described.¹⁴

To assess the electromechanical delay of the LA, the PA-TDI duration was measured from color-coded TDI data. The PA-TDI duration is a surrogate of the total atrial conduction time (which is considered a surrogate for LA fibrosis) and has been associated with the occurrence of AF in various cardiac diseases.^{6,15-17} To measure the PA-TDI duration, a sample volume is placed on the lateral wall of the LA just above the mitral annulus to provide the tracing of the mechanical activation in that area. The PA-TDI duration was assessed by measuring the time interval between the onset of the P-wave on the surface ECG and the peak of the A'-wave on color-coded TDI tracing (Figure 1).

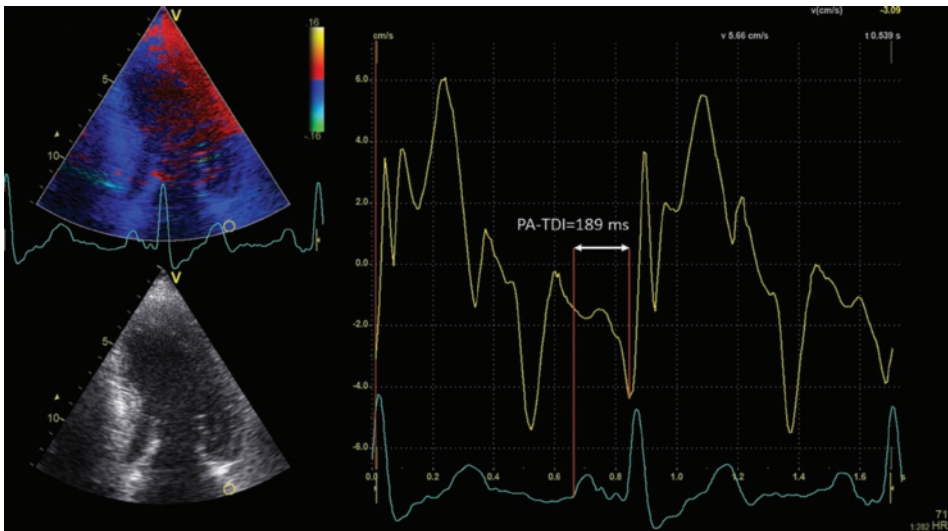


Figure 1. Measurement of PA-TDI (tissue Doppler imaging) duration in a patient with end-stage renal disease. The sample volume is placed on the lateral wall of the left atrium just above the mitral annulus and the PA-TDI duration is measured as the time interval between the onset of the P-wave (derived from the ECG tracing) and the peak of the A'-wave on color-coded TDI. The PA-TDI duration in this patient was 189 ms. This patient developed atrial fibrillation during follow-up.

Atrial fibrillation

The occurrence of AF was detected based on ICD remote monitoring or clinical records. All ICDs were dual-chamber (Biotronik, Berlin, Germany), implanted

transvenously and fitted with an external remote monitoring device (Biotronik, Cardiomessenger 2-S). The ICD evaluated all P-P intervals and was programmed to register an atrial episode if at least 36 out of 48 consecutive P-P intervals had a frequency higher than 180/min. An atrial episode was deemed terminated if 20 out of 24 consecutive P-P intervals had a frequency of <180/min. All atrial episodes were analysed using the remotely transmitted intracardiac electrogram and analysed to detect those that were AF. The type of AF was diagnosed according to current recommendations.¹⁸

Statistical analysis

All continuous variables were tested for a normal distribution using the Kolmogorov-Smirnov test. Categorical variables are presented as numbers and percentages. Continuous variables with a normal distribution are presented as the mean $\pm$ standard deviation and those without a normal distribution are presented as the median and interquartile range. Differences between patients with and without AF were evaluated using the unpaired Student's t test or Mann-Whitney U test, as appropriate for continuous data. For categorical data, the chi-square test was used and for small numbers, the Fisher's exact test. Binary logistic regression was applied in a multivariate model to explore independent correlates of AF in this population. Statistical analyses were performed using the SPSS software (Version 20.0. Armonk, NY: IBM Corp). All statistical tests were 2-sided and a P-value of <0.05 was considered significant.

RESULTS

A total of 171 patients were included (129 men (75%), mean age 67 ± 7 years). Fourteen patients were excluded due to the absence of sinus rhythm during the echocardiographic examination. Among the included patients, 47 patients (27%) experienced AF. Differences in clinical and ECG characteristics between patients with and without AF are listed in Table 1. Patients with AF showed significantly higher use of sotalolol (7 (15) vs. 1 (1) %, $p=0.001$) and oral anticoagulation (12 (26) vs. 9 (7) %, $p=0.001$), higher plasma levels of sodium (140 ± 3 vs. 139 ± 3 mmol/L, $p=0.008$), lower heart rate (67 ± 10 vs. 72 ± 12 beats/min, $p=0.005$), longer QT interval (417 ± 52 vs. 394 ± 37 ms, $p=0.002$) and corrected QT interval ($418 (409-452)$ vs. $412 (399-433)$ ms, $p=0.033$) compared to the group without AF.

Among the patients with AF, 31 patients (66%) had paroxysmal AF, 11 persistent AF (23%) and 5 permanent AF (11%). Twenty-two patients (47%) experienced AF before study entry.

Table 1. Characteristics of end-stage renal disease patients with and without AF

	AF (n=47)	No AF (n=124)	P value
<u>Clinical characteristics:</u>			
Age (years)	68 ± 7	67 ± 7	0.285
Male gender, n (%)	39 (83)	90 (73)	0.158
Dialysis type (hemodialysis), n (%)	35 (75)	86 (69)	0.512
Dialysis vintage, months	17 (11-32)	14 (7-26)	0.159
Body mass index (kg/m ²)	28 ± 5	27 ± 4	0.066
Smoking, n (%)	31 (66)	83 (67)	0.904
Diabetes mellitus, n (%)	20 (43)	43 (35)	0.341
Hypertension, n (%)	38 (81)	100 (81)	0.976
Hypercholesterolemia, n (%)	25 (53)	61 (49)	0.641
Previous myocardial infarction, n (%)	12 (26)	37 (30)	0.578
Previous CABG or PCI, n (%)	10 (21)	36 (29)	0.294
<u>Medication:</u>			
ACE inhibitor/ARB, n (%)	28 (60)	59 (48)	0.161
Calcium antagonist, n (%)	17 (36)	45 (36)	0.988
β Blocker, n (%)	28 (60)	72 (58)	0.858
Sotalol, n (%)	7 (15)	1 (1)	0.001
Amiodarone, n (%)	1 (2)	1 (1)	0.475
Oral anticoagulation, n (%)	12 (26)	9 (7)	0.001
Statin, n (%)	28 (60)	80 (65)	0.550
<u>Laboratory results:</u>			
RRF (ml/min/1.73m ²)	2.1 (1.2-2.7)	1.6 (0.0-2.7)	0.094
Sodium (mmol/L)	140 ± 3	139 ± 3	0.008
Potassium (mmol/L)	4.8 (4.4-5.4)	4.7 (4.2-5.2)	0.660
Phosphate (mmol/L)	1.5 ± 0.4	1.5 ± 0.4	0.864
Corrected calcium (mmol/L)	2.3 ± 0.2	2.3 ± 0.2	0.578
Parathyroid hormone (pmol/L)	26 (15-57)	24 (14-40)	0.544
Hemoglobin (mmol/L)	7.5 ± 0.7	7.6 ± 0.8	0.466

Table 1. Continued

	AF (n=47)	No AF (n=124)	P value
<u>Electrocardiogram:</u>			
Heart rate (beats/min)	67 ± 10	72 ± 12	0.005
P-wave duration (ms)	106 ± 21	106 ± 17	0.908
PR interval (ms)	178 (162-201)	171 (160-189)	0.147
QRS duration (ms)	101 ± 19	101 ± 15	0.850
QT interval (ms)	417 ± 52	394 ± 37	0.002
Corrected QT interval (ms)	418 (409-452)	412 (399-433)	0.033

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; RRF, residual renal function.

Continuous data are presented as mean ± SD or median (interquartile range). Categorical data are presented as numbers and percentages.

Regarding the echocardiographic characteristics, patients with AF had significantly larger LV end-diastolic and end-systolic diameters and larger end-diastolic volume compared with their counterparts (Table 2). Furthermore patients with AF had significantly larger LA volume index (29 ± 11 vs. 23 ± 10 mL/m², $p=0.001$), reduced late diastolic mitral annular velocity (A') (7.1 ± 2.8 vs. 8.2 ± 2.4 cm/s, $p=0.012$) and longer PA-TDI duration (144 ± 30 vs. 131 ± 27 ms, $p=0.010$) compared to patients without AF. There were no differences in LV ejection fraction or presence of mitral regurgitation.

Correlates of AF

On multivariable analysis, larger LA volume index (odds ratio [OR] 1.04, 95% confidence interval [CI] 1.01-1.08, $p=0.017$), longer PA-TDI duration (OR 1.02, 95% CI 1.00-1.03, $p=0.025$) and reduced late diastolic mitral annular velocity (OR 0.84, 95% CI 0.72-0.98, $p=0.025$), were independently associated with AF after adjusting for age and LV diastolic relaxation (Table 3).

Table 2. Echocardiographic characteristics of end-stage renal disease patients with and without AF

	AF (n=47)	No AF (n=124)	Normal reference range 11,14	P value
IVSTd (mm)	12 ± 2	12 ± 3	6-10	0.787
PWTd (mm)	11 ± 2	11 ± 2	6-10	0.321
LVEDD (mm)	52 ± 6	49 ± 7	38-58	0.009
LVESD (mm)	37 ± 8	34 ± 7	22-40	0.017
LVEDV (ml)	133 ± 47	114 ± 39	48-185	0.008
LVESV (ml)	54 (43-73)	46 (37-64)	12-78	0.117
LVEF (%)	56 ± 8	54 ± 8	46-78	0.115
LAVI (mL/m ²)	29 ± 11	23 ± 10	16-34	0.001
TAPSE (mm)	22 ± 3	21 ± 4	>17	0.084
Moderate/severe MR, n (%)	8 (17)	12 (10)		0.165
Tricuspid regurgitation (mmHg)	25 ± 8	25 ± 8	<32	0.813
Maximal E-wave velocity (m/s)	0.8 ± 0.3	0.7 ± 0.2		0.220
Maximal A-wave velocity (m/s)	0.8 ± 0.3	0.9 ± 0.2		0.069
Lateral E' (cm/s)	6.2 ± 2.5	5.9 ± 2.1		0.459
Lateral A' (cm/s)	7.1 ± 2.8	8.2 ± 2.4		0.012
PA-TDI (ms)	144 ± 30	131 ± 27		0.010

AF, atrial fibrillation; IVSTd, interventricular septum width; LAVI, left atrial volume index; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end diastolic diameter; LVEDV, left ventricular end diastolic volume; LVESD, left ventricular end systolic diameter; LVESV, left ventricular end systolic volume; MR, mitral regurgitation; PWTd, posterior wall width; TAPSE, tricuspid annular plane systolic excursion; TDI, tissue Doppler imaging. Continuous data are presented as mean ± SD or median (interquartile range). Categorical data are presented as numbers and percentages.

DISCUSSION

The present study demonstrated that ESRD patients with AF versus patients without AF have significantly larger LA volume index, reduced late diastolic mitral annular velocity (A', reflecting atrial booster pump function) and longer PA-TDI duration. These echocardiographic differences suggest that patients with ESRD and AF have LA structural changes (i.e. LA dilatation, and possibly fibrosis – as

reflected by increased PA-TDI) that lead to reduced LA function (A' reflecting active atrial contribution to LV filling) as compared to ESRD patients without AF.

Table 3. Significant correlates of atrial fibrillation in all end-stage renal disease patients

	OR (95% CI)	P value
Age (years)	1.03 (0.98-1.09)	0.272
PA-TDI (ms)	1.02 (1.00-1.03)	0.026
Left atrium volume index (mL/m ²)	1.04 (1.01-1.08)	0.017
Lateral A' (cm/s)	0.84 (0.72-0.98)	0.025
Lateral E' (cm/s)	1.19 (0.995-1.42)	0.057

CI, confidence interval; OR, odds ratio; TDI, tissue Doppler imaging.

Prevalence of AF in ESRD patients

Similar to the general population, AF is the most common arrhythmia among patients with ESRD. In a recent meta-analysis including 253,589 ESRD patients across 25 studies, the prevalence of AF was 11.6% (range 5.4-27%).¹ The wide range in prevalence of AF across the different studies may be explained by the different study designs (i.e. retrospective versus prospective), classification of AF (i.e. paroxysmal versus persistent AF, valvular versus non-valvular) and detection of AF (self-reported episodes of AF versus documentation of AF with ECG, Holter recordings or remote monitoring device). A recent study including 63,884 ESRD patients from Medicare and Medicaid populations who were selected based on the presence of chronic AF documented for at least 3 months during a 2-year window (paroxysmal AF, patients with valvular heart disease, hyperthyroidism or who underwent cardiac surgery were excluded) reported a prevalence of chronic AF of 7%,¹⁹ a rate ten-fold higher than that observed in the general population.²⁰ In the present study, the prevalence of AF was 27%, compatible with 2 of the 25 studies included in the meta-analysis by Zimmerman et al.^{21,22} The inclusion of any type of AF and the methodology used in the current study to detect AF episodes included remote monitoring devices, which provide the most sensitive approach to detect even asymptomatic episodes of AF, may have contributed to the higher prevalence compared with those reported in previous studies.^{1,19} Furthermore, several demographic and clinical characteristics associated with increased risk of AF may be different across the studies, explaining the differences in AF prevalence. Age, hypertension and diabetes mellitus are important risk factors

for AF development in ESRD, which were highly prevalent in the present study population. In addition, the present study included a significant proportion of patients with moderate and severe mitral valve regurgitation, which is associated with AF.

These risk factors contribute to LA structural remodeling and pave the substrate for AF.⁴ In addition, AF itself may induce structural remodeling of the LA perpetuating the arrhythmia.²³ The hemodynamic and metabolic disturbances that may occur in ESRD patients, such as increased sympathetic tone, renin-angiotensin-aldosterone system activation, changes in volume and pressure overload, oxidative stress and inflammation may lead to atrial remodeling and modulate the LA arrhythmogenic substrate enhancing the risk of AF.^{5,24} Echocardiography permits thorough evaluation of the LA structural and functional changes that may lead to AF. However, the association between echocardiographic LA parameters and AF in ESRD patients remained unexplored.

Left atrial remodeling in ESRD patients with versus without AF

Large LA volume, the extent of LA fibrosis and reduced LA function reflect the LA remodeling process that may lead to development and perpetuation of AF. Increased LA dimensions (linear or volumetric measurements) have been consistently associated with high risk of new onset AF and progression to permanent AF.^{25,26} Furthermore, LA dilatation is accompanied by interstitial myocardial fibrosis and increased collagen content, which is the hallmark of the LA structural remodeling leading to AF.

Importantly, ESRD patients have additional risk factors that promote myocardial interstitial fibrosis and perivascular fibrosis such as uremia, chronic anemia and hyperparathyroidism.²⁷⁻²⁹ In the current study, echocardiographic variables reflecting LA dilatation, fibrosis and reduced function were all significantly altered in ESRD patients with AF versus patients without AF. Echocardiographic assessment of LA dilatation is most often measured with 2-dimensional linear diameters. However, the dilatation of the LA is a 3-dimensional process and therefore in the current study volumetric assessment of the LA was applied, which may better reflect the LA dilatation.²⁶ This approach has better correlation with other imaging modalities (magnetic resonance imaging), that measure the LA size in 3-dimensions.³⁰ In addition, LA fibrosis was assessed by measuring the PA-TDI duration, a parameter that estimates the electrical-mechanical conduction delay.³¹ In a study including 495 heart failure patients treated with an ICD, 29%

of patients experienced AF during a mean follow-up of 16 months and showed significantly longer PA-TDI duration as compared with patients without AF occurrence (154 ± 27 vs. 135 ± 24 ms, respectively; $p < 0.001$).¹⁶ In the present study, ESRD patients who presented with AF had significantly longer PA-TDI duration compared with patients who remained in sinus rhythm, suggesting that more advanced LA fibrosis is present in this subgroup of patients.

LA dilatation and fibrosis lead to impaired LA function^{32,33}; in the current study LA function was measured with load-independent TDI-derived A' , which reflects the contraction of the LA during late diastole. This parameter may be a better measure of the function of the LA, rather than volumetric measures in ESRD patients.³⁴ The clinical implications of assessment of A' have been demonstrated in several studies.^{35,36} In 518 patients (68% of patients with various cardiac diseases), a value of $A' \leq 4$ cm/s was significantly associated with increased risk of cardiac death (hazard ratio 5.2, 95% CI 2.48-10.2) on univariate analysis.³⁵

Conclusion

ESRD patients with AF have more advanced changes in the LA substrate, comprising LA dilatation, increased LA fibrosis and reduced LA function.

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Chapter 8

SUMMARY CONCLUSIONS AND
FUTURE PERSPECTIVES

SUMMARY, CONCLUSIONS AND FUTURE PERSPECTIVES

Summary

The general introduction (**Chapter 1**) of this thesis provides an overview of the cardiovascular diseases associated with chronic kidney disease (CKD) described in this thesis. Patients with CKD have an increased risk of cardiovascular morbidity and mortality. Heart failure, ventricular arrhythmias, sudden cardiac death, valvular heart disease, valvular calcium and atrial fibrillation are particularly frequent in patients with advanced CKD, due to hemodynamic and metabolic disturbances. Conventional two-dimensional echocardiography is the imaging technique of first choice to evaluate these patients, including assessment of left ventricular (LV) volumes and ejection fraction (EF), diastolic function and significant valvular heart disease. In addition, the role of advanced echocardiographic imaging techniques including two-dimensional speckle tracking echocardiography and coronary computed tomography angiography (CTA) is introduced. The current thesis aims at evaluating cardiac mechanics using two-dimensional (speckle tracking) echocardiography and coronary CTA in patients with CKD to define the prevalence and prognostic implications of cardiovascular diseases.

Part I: Left ventricular systolic dysfunction in chronic kidney disease

In the first part advanced echocardiographic techniques are used to address the prevalence of subtle LV systolic dysfunction and LV mechanical dyssynchrony in patients with advanced CKD and its prognostic implications. Furthermore the prognostic implications of LV global longitudinal strain (GLS) were evaluated.

CKD patients may have heart failure symptoms with preserved LVEF. In this subgroup of patients, 2-dimensional speckle tracking echocardiography can detect LV systolic dysfunction by analysing LV myocardial deformation. Pre-dialysis and dialysis patients with CKD stage 3b-5 and preserved LVEF (LVEF $\geq 50\%$) were evaluated. LV systolic dysfunction despite preserved LVEF was defined by LV GLS $\leq 15.2\%$ (cut-off value derived from the 2 standard deviations below the mean value of individuals without structural heart disease). Impaired LV GLS ($\leq 15.2\%$) despite preserved LVEF was observed in 32% of patients. Patients with preserved LVEF but impaired LV GLS had an increased risk of HF hospitalisation and all-cause mortality (**Chapter 2**).

LV GLS is a measure of LV systolic function associated with prognosis in the general population. However, little is known about the association between LV

GLS and survival in patients with CKD. LV GLS was measured in a retrospective cohort of pre-dialysis and dialysis patients (CKD stage 3b-5) and patients were divided into 4 groups according to quartiles of LV GLS. LV GLS $\leq$ 10.6% was significantly associated with increased risk of all-cause mortality after correcting for age, gender, albumin levels, atrial fibrillation and renal transplantation **(Chapter 3)**.

Patients with advanced CKD have high risk of sudden cardiac death and may benefit from an implantable cardioverter defibrillator (ICD). However, the risk of ICD-related complications is also high in this population. Therefore, there is an unmet need for accurate risk stratification tools to identify CKD patients at risk of ventricular arrhythmias, who may benefit from ICD implantation. LV mechanical dispersion along with LV GLS may be an additional valuable risk marker of ventricular arrhythmias and sudden cardiac death in pre-dialysis and dialysis patients **(Chapter 4)**.

Part II: Valvular heart disease in chronic kidney disease

The second part describes the role of conventional echocardiography and coronary CTA in addressing the burden of valvular heart disease and left-sided valve calcium and its prognostic implications in patients with CKD.

Patients with CKD have an increased risk for valvular heart disease due to hemodynamic factors and metabolic pathways that promote valvular calcification and dysfunction. The prevalence of valvular heart disease in patients with CKD however, is unclear. The prevalence of significant valvular heart disease in pre-dialysis and dialysis patients was 26%. Surgical or transcatheter valve replacement or repair was performed infrequently. Patients with significant valvular heart disease had significantly increased risk of all-cause mortality compared to patients without significant valvular heart disease **(Chapter 5)**.

In CKD patients, valvular calcium is an important underlying mechanism of valve dysfunction. In patients with stage 2 and 3 CKD who underwent clinically indicated coronary CTA, the presence of mitral and/or aortic valve calcium was assessed. Patients with mitral and/or aortic valve calcium showed significantly higher mortality rates compared to patients without left-sided valve calcium. Mitral valve calcium was independently associated with increased risk of all-cause mortality, whereas aortic valve calcium was not **(Chapter 6)**.

Part III: Atrial fibrillation in chronic kidney disease

The third part describes the role of conventional echocardiography in characterising the left atrium in patients with atrial fibrillation and end-stage renal disease.

The prevalence of atrial fibrillation in end-stage renal disease patients is relatively high. Electrical and structural remodeling of the atrial myocardium serves as a substrate for atrial fibrillation. However, the structural remodeling of the left atrium has not been characterized in this group of patients. In end-stage renal disease patients the left atrial dimensions, left atrial conduction delay (as reflected by the time difference between P-wave onset on surface electrocardiogram and A'-wave on tissue Doppler imaging [PA-TDI]) and left atrial function were compared between patients who exhibited atrial fibrillation versus patients without atrial fibrillation. End-stage renal disease patients with atrial fibrillation had more advanced changes in the left atrial substrate, comprising left atrial dilatation, increased left atrial fibrosis and reduced left atrial function (**Chapter 7**).

Conclusions and future perspectives

The burden of cardiovascular diseases in patients with CKD is high and thorough assessment of cardiac mechanics with (advanced) echocardiographic techniques and coronary CTA helps in identifying patients with worse prognosis, who would potentially benefit of early treatment.

In pre-dialysis and dialysis patients with preserved LVEF, assessment of LV GLS helps to identify patients with higher rates of heart failure hospitalisation and all-cause mortality. Prospective studies may answer the question whether implementation of heart failure therapy on top of optimal control of cardiovascular risk factors at this early stage of LV systolic dysfunction would result in improved outcome. When LVEF has already declined, patients within the lowest quartile of LV GLS showed worse prognosis compared to the other groups, even after correcting for renal transplantation. This is clinically relevant since renal transplantation is considered a life-saving treatment in these patients and proper selection of patients receiving a renal transplant is crucial to optimize the results of this therapy. Whether LV GLS improves after renal transplantation has not been evaluated. LV mechanical dispersion along with LV GLS may be an additional valuable risk marker of ventricular arrhythmias and sudden cardiac death in pre-dialysis and dialysis patients. However, the relatively small number of

patients presenting with events precluded us of performing multivariate analysis to investigate the independent association of advanced echocardiographic parameters and the occurrence of ventricular arrhythmias and sudden cardiac death. Larger prospective studies are needed to investigate the role of strain echocardiography in risk stratification of sudden cardiac death in patients with advanced CKD.

Patients with significant valvular heart disease have an increased risk for all-cause mortality, partly due to the low percentage of surgical or transcatheter valve replacement or repair in these patients. The high mortality risk in patients with CKD and significant valvular heart disease indicates the importance of appropriate treatment of these patients. Prospective studies are needed to investigate the role of transcatheter valve replacement and repair in patients with CKD and severe valvular heart disease. In CKD patients, valvular calcium is an important underlying mechanism of valve dysfunction. The presence of mitral and/or aortic valve calcium was associated with poor survival in this population. The high mortality risk in patients with CKD and left-sided valve calcium underscores the importance of appropriate treatment of these patients. Future studies are needed to investigate the association between mitral valve calcium and CKD and subsequently potential therapeutic targets to prevent valvular calcium.

End-stage renal disease patients with atrial fibrillation have more advanced changes in the left atrial substrate, comprising left atrial dilatation, increased left atrial fibrosis and reduced left atrial function. Prospective studies are needed to investigate potential therapeutic regimens to prevent left atrial remodeling.

Chapter 9

SAMENVATTING, CONCLUSIES EN
TOEKOMSTPERSPECTIEVEN

SAMENVATTING, CONCLUSIES EN TOEKOMSTPERSPECTIEVEN

Samenvatting

De algemene inleiding (**Hoofdstuk 1**) van dit proefschrift geeft een overzicht van de cardiovasculaire aandoeningen geassocieerd met chronische nierinsufficiëntie (CNI) beschreven in dit proefschrift. Patiënten met CNI hebben een verhoogd risico op cardiovasculaire morbiditeit en mortaliteit. Hartfalen, ventriculaire aritmieën, plotse hartdood, hartklepaandoeningen, klepcalcium en atriumfibrilleren komen vaak voor bij patiënten met gevorderde CNI, als gevolg van hemodynamische en metabole stoornissen. Conventionele tweedimensionale echocardiografie is de eerste keus beeldvorming om deze patiënten te evalueren, waaronder de beoordeling van de volumes en ejectiefractie (EF) van de linker ventrikel (LV), de diastolische functie en de klepfunctie. Bovendien wordt de rol van geavanceerde echocardiografische beeldvormingstechnieken waaronder tweedimensionale speckle tracking echocardiografie en coronaire computertomografie-angiografie (CTA) geïntroduceerd. Het huidige proefschrift is gericht op het evalueren van cardiale mechanica met behulp van tweedimensionale (speckle tracking) echocardiografie en coronaire CTA bij patiënten met CNI om de prevalentie en prognostische implicaties van hart- en vaatziekten te bepalen.

Deel I: Linker ventrikel systolische dysfunctie bij chronische nierinsufficiëntie

In het eerste deel worden geavanceerde echocardiografische technieken gebruikt om de prevalentie van subtiele LV systolische dysfunctie en LV mechanische dyssynchronie te beschrijven bij patiënten met gevorderde CNI en de prognostische implicaties daarvan. Verder worden de prognostische implicaties van LV globale longitudinale strain (GLS) geëvalueerd.

Patiënten met chronische nierinsufficiëntie kunnen hartfalen hebben met behouden LVEF. In deze subgroep van patiënten, kan tweedimensionale speckle tracking echocardiografie LV systolische dysfunctie detecteren door de LV myocardiale vervorming te analyseren. Pre-dialyse en dialyse patiënten met CNI stadium 3b-5 en behouden LVEF (LVEF $\geq 50\%$) werden geëvalueerd. LV systolische dysfunctie ondanks behouden LVEF werd gedefinieerd als LV GLS $\leq 15,2\%$ (afkapwaarde afgeleid van 2 standaarddeviaties onder de gemiddelde waarde van individuen zonder structurele hartziekte). Verminderde LV GLS ($\leq 15,2\%$) ondanks een behouden LVEF werd waargenomen bij 32% van de patiënten. Patiënten met een behouden LVEF maar met een verminderde LV

GLS hadden een verhoogd risico op een ziekenhuisopname door hartfalen en op mortaliteit **(Hoofdstuk 2)**.

LV GLS is een maat voor LV systolische functie geassocieerd met prognose in de algemene populatie. Er is echter weinig bekend over de associatie tussen LV GLS en overleving bij patiënten met CNI. LV GLS werd gemeten in een retrospectief cohort van pre-dialyse- en dialysepatiënten (CKD stadium 3b-5) en de patiënten werden verdeeld in 4 groepen volgens kwartielen van LV GLS. LV GLS $\leq$ 10,6% was significant geassocieerd met een verhoogd risico op mortaliteit na correctie voor leeftijd, geslacht, albumine, atriumfibrillatie en niertransplantatie **(Hoofdstuk 3)**.

Patiënten met gevorderde CNI hebben een hoog risico op plotse hartdood en kunnen baat hebben bij een implanteerbare cardioverter defibrillator (ICD). Het risico van ICD-gerelateerde complicaties is echter ook hoog in deze populatie. Daarom is er een on vervulde behoefte aan nauwkeurige risicostratificatie middelen om patiënten met CNI die risico lopen op ventriculaire aritmieën en baat kunnen hebben bij een ICD, te identificeren. LV mechanische dispersie samen met LV GLS kan een additionele waardevolle risicomarker zijn voor ventriculaire aritmieën en plotse hartdood in pre-dialyse en dialyse patiënten **(Hoofdstuk 4)**.

Deel II: Hartklepziekten bij chronische nierinsufficiëntie

Het tweede deel beschrijft de rol van conventionele echocardiografie en coronaire CTA bij het beschrijven van de ernst van hartklepaandoeningen en linkszijdig klepcalcium bij patiënten met CNI en de prognostische implicaties hiervan.

Patiënten met CNI hebben een verhoogd risico op hartklepaandoeningen vanwege hemodynamische en metabole factoren die klepverkalking en dysfunctie bevorderen. De prevalentie van hartklepaandoeningen bij patiënten met CNI is echter onduidelijk. De prevalentie van significante hartklepaandoeningen bij pre-dialyse en dialysepatiënten was 26%. Chirurgische of transkatheterklep vervanging of reparatie werd niet vaak uitgevoerd. Patiënten met significante hartklepaandoeningen hadden een significant verhoogd risico op mortaliteit in vergelijking met patiënten zonder significante hartklepaandoening **(Hoofdstuk 5)**.

Bij patiënten met CNI is klepcalcium een belangrijk onderliggend mechanisme van klepdysfunctie. Bij patiënten met stadium 2 en 3 CNI die een klinisch geïndiceerd coronaire CTA ondergingen, werd de aanwezigheid van mitralis- en/of aortaklepcalcium vastgesteld. Patiënten met mitralis- en/of aortaklepcalcium

vertoonden significant hogere sterftecijfers in vergelijking met patiënten zonder linkszijdig klepcalcium. Mitralisklepcalcium was onafhankelijk geassocieerd met een verhoogd risico op mortaliteit, terwijl aortaklepcalcium dit niet was (**Hoofdstuk 6**).

Deel III: Boezemfibrilleren bij chronische nierinsufficiëntie

Het derde deel beschrijft de rol van conventionele echocardiografie bij het karakteriseren van het linker atrium bij patiënten met atriumfibrilleren en terminale nierinsufficiëntie.

De prevalentie van atriumfibrilleren bij patiënten met eindstadium nierfalen is relatief hoog. Elektrische en structurele remodelering van het atriummyocard dient als een substraat voor atriumfibrilleren. De structurele remodelering van het linker atrium is echter niet gekarakteriseerd in deze groep patiënten. Bij patiënten met eindstadium nierfalen werden de dimensies van het linker atrium, geleidingsvertraging van het linker atrium (zoals weerspiegeld door het tijdsverschil tussen het begin van de P-golf op het oppervlakte elektrocardiogram en de A'-golf bij tissue-Doppler-imaging [PA-TDI]) en de functie van het linker atrium vergeleken tussen patiënten met en zonder atriumfibrilleren. Patiënten met eindstadium nierfalen en atriumfibrilleren hadden verder gevorderde veranderingen in het substraat van het linker atrium, bestaande uit linker atriumdilatatie, toegenomen linker atrium fibrose en verminderde linker atrium functie (**Hoofdstuk 7**).

Conclusies en toekomstperspectieven

De belasting van hart- en vaatziekten bij patiënten met CNF is hoog en een grondige beoordeling van de cardiale mechanica met (geavanceerde) echocardiografische technieken en coronaire CTA helpt bij het identificeren van patiënten met een slechtere prognose, die mogelijk voordeel zouden kunnen hebben van een vroege behandeling.

Bij pre-dialyse- en dialysepatiënten met een behouden LVEF helpt de beoordeling van LV GLS bij het identificeren van patiënten met meer ziekenhuisopnames door hartfalen en een hogere mortaliteit. Prospectieve studies kunnen de vraag beantwoorden of de implementatie van hartfalen therapie bovenop de optimale controle van cardiovasculaire risicofactoren in dit vroege stadium van LV systolische disfunctie zou resulteren in een verbeterde prognose. Wanneer LVEF al was afgenomen, hadden patiënten met het

laagste LV GLS kwartiel een slechtere prognose in vergelijking met de andere groepen, zelfs na correctie voor niertransplantatie. Dit is klinisch relevant, omdat niertransplantatie bij deze patiënten als een levensreddende behandeling wordt beschouwd en een goede selectie van patiënten die een niertransplantatie ondergaan cruciaal is om de resultaten van deze therapie te optimaliseren. Of LV GLS verbetert na niertransplantatie is niet geëvalueerd. LV mechanische dispersie samen met LV GLS kan een additionele waardevolle risicomarker zijn voor ventriculaire aritmieën en plotse hartdood bij pre-dialyse en dialysepatiënten. Het relatief kleine aantal patiënten met eindpunten, weerhield ons echter van het uitvoeren van multivariate analyse om de onafhankelijke associatie van geavanceerde echocardiografische parameters en het optreden van ventriculaire aritmieën en plotse hartdood te onderzoeken. Grotere prospectieve studies zijn nodig om de rol van strain echocardiografie bij de risicostratificatie van plotse hartdood bij patiënten met gevorderde CNI te onderzoeken.

Patiënten met een significante hartklepaandoening hebben een verhoogd risico op mortaliteit, gedeeltelijk als gevolg van het lage percentage chirurgische of transkatheter klepvervanging of reparatie bij deze patiënten. Het hoge sterfterisico bij patiënten met CNI en significante hartklepaandoeningen geeft het belang aan van een passende behandeling van deze patiënten. Prospectieve studies zijn nodig om de rol van transkatheter klepvervanging en reparatie bij patiënten met CNI en ernstige hartklepaandoeningen te onderzoeken. Bij patiënten met CNI is klepcalcium een belangrijk onderliggend mechanisme van klepdysfunctie. De aanwezigheid van calcium op de mitralis en/of aortaklep in deze populatie was geassocieerd met een slechte overleving. Het hoge sterfterisico bij patiënten met CNI en linkszijdig klepcalcium onderstreept het belang van een gepaste behandeling van deze patiënten. Toekomstige studies zijn nodig om de associatie tussen mitralisklepcalcium en CNI te onderzoeken en om potentiële therapeutische doelwitten te vinden om het klepcalcium te voorkomen.

Patiënten met eindstadium nierfalen en atriumfibrilleren hebben verder gevorderde veranderingen in het substraat van het linker atrium, bestaande uit linker atrium dilatatie, meer fibrose van het linker atrium en een verminderde functie van het linker atrium. Prospectieve studies zijn nodig om mogelijke therapeutische regimes te onderzoeken om remodellering van het linker atrium te voorkomen.

Appendix

LIST OF PUBLICATIONS

Hensen LCR, Delgado V, van Wijngaarden SE, Leung M, de Bie MK, Buiten MS, SchaliJ MJ, van de Kerkhof JJ, Jukema JW, Rabelink TJ, Rotmans JI, Bax JJ. Echocardiographic associates of atrial fibrillation in end-stage renal disease. *Nephrol Dial Transplant*. 2017; 32(8): 1409-1414.

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Hensen LCR, el Mahdiui M, van Rosendael AR, Smit JM, Jukema JW, Bax JJ, Delgado V. Prevalence and prognostic implications of mitral and aortic valve calcium in patients with chronic kidney disease. *Am J Cardiol*. 2018; 122(10): 1732-1737.

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CURRICULUM VITAE

Liselotte Catharina Rosalina Hensen werd geboren op 23 mei 1989 in Heemstede. In 2007 behaalde zij haar gymnasiumdiploma aan het Lyceum Sancta Maria te Haarlem. Van 2007 tot en met 2013 studeerde zij geneeskunde aan de Universiteit Leiden. Tijdens haar bachelor- en masterfase was zij betrokken bij wetenschappelijk onderzoek, naar de vetstapeling in andere weefsels dan vetweefsel in diabetes en obesitas, onder leiding van dr. J.T. Jonker, prof. dr. J.W.A. Smit en prof. dr. J.A. Romijn, op de afdeling endocrinologie van het Leids Universitair Medisch Centrum (LUMC). Na het behalen van haar master in 2013, startte zij in januari 2014 als arts niet in opleiding tot specialist (ANIOS) op de afdeling cardiologie van het LUMC. Na dit acht maanden te hebben gedaan, begon zij met haar promotieonderzoek op dezelfde afdeling, onder leiding van prof. dr. J.W. Jukema, prof. dr. J.J. Bax en dr. J.I. Rotmans. De resultaten van dit onderzoek staan beschreven in dit proefschrift. Na haar tijd als arts-onderzoeker heeft zij een jaar als ANIOS gewerkt in het HagaZiekenhuis te Den Haag. Per 1 oktober 2018 is zij begonnen met de opleiding cardiologie vanuit het HagaZiekenhuis (opleider dr. J.W.J. Vriend) en is zij momenteel werkzaam in het Onze Lieve Vrouwe Gasthuis locatie Oost te Amsterdam, alwaar zij de vooropleiding interne geneeskunde volgt (opleider dr. Y.F.C. Smets).

