Left ventricular mechanical dispersion and global longitudinal strain 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.

Keywords: Chronic kidney disease, sudden cardiac death, strain, LV mechanical dispersion

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 cineloop 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 (including the apex) 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).

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 ± 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. ROC

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.

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.

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 ≤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 ≤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 unmasks 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.

Although LV mechanical dispersion could be considered a marker of LV mechanical dyssynchrony, since it is calculated as the standard deviation of time to peak longitudinal strain of 17 segments (according to the commercially available software used in this study), the term LV mechanical dyssynchrony is more frequently used in patients with heart failure who may be candidates for cardiac resynchronization therapy (which aims at resynchronizing the contraction of the LV). LV mechanical dispersion, as a measure of the temporal heterogeneity of the mechanical contraction of the LV, has been tested in a broader spectrum of patients who are at increased risk of VA/SCD (long-QT syndrome, acute myocardial infarction patients) and do not need per se a cardiac resynchronization therapy device.[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 with commercially available software. The results therefore may not be generalizable when other manufacturers are used. 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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None

Conflict of interest

V. Delgado received speaking fees from Abbott Vascular. The other authors have no conflicts of interest to declare.

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Legends

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% (absolute value) in a pre-dialysis patient with sustained ventricular tachycardia during follow-up.

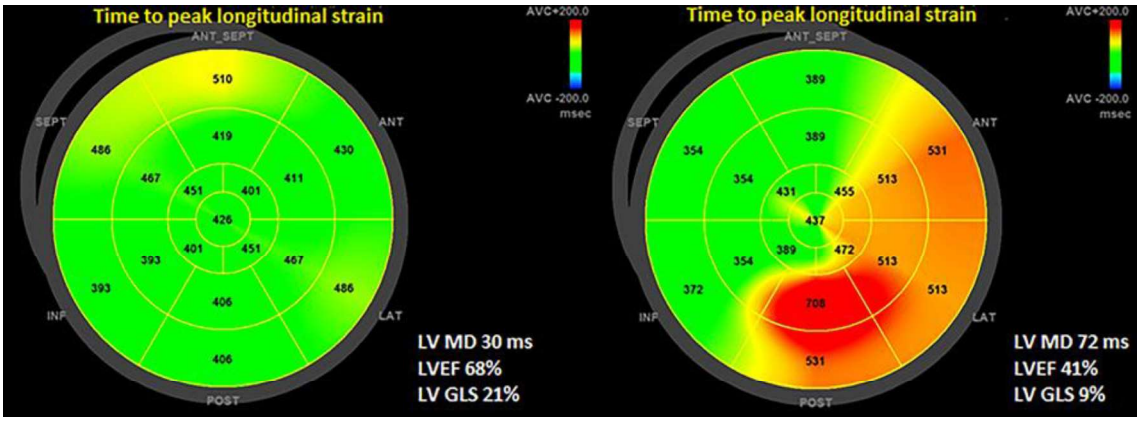

Figure 2. Box plots of left ventricular (LV) global longitudinal strain (GLS), LV mechanical dispersion (MD) and LV ejection fraction (LVEF) in pre-dialysis and dialysis patients with and without ventricular arrhythmia (VA) or sudden cardiac death (SCD) during follow-up. Absolute LV GLS was significantly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

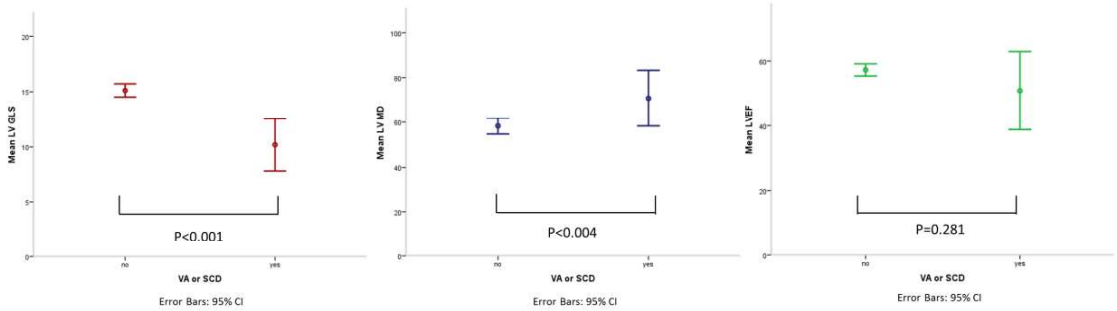

Figure 3. Receiver operating characteristic curve analysis demonstrating the ability of left ventricular (LV) mechanical dispersion (MD), LV ejection fraction (LVEF) and LV global longitudinal strain (GLS) to predict ventricular arrhythmia (VA) or sudden cardiac death (SCD) in pre-dialysis and dialysis 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).

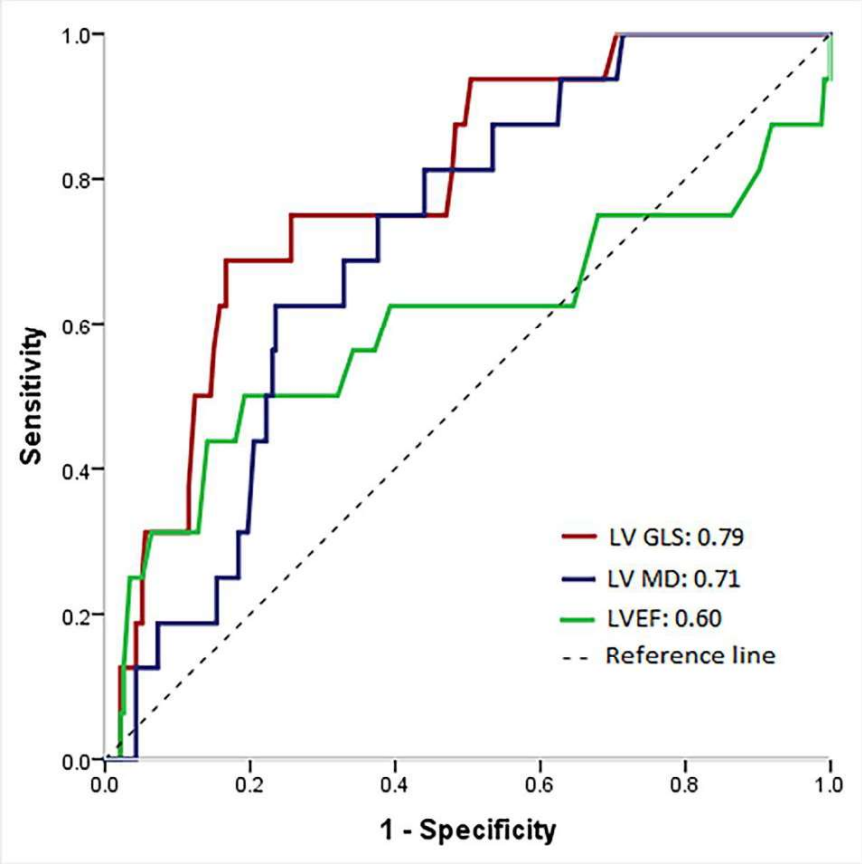

Table 1. Characteristics of pre-dialysis and dialysis patients with and without ventricular arrhythmias or sudden cardiac death during follow-up.

Variable	Patients without VA or SCD (n=234)	Patients with VA or SCD (n=16)	P value
Clinical characteristics:			
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/m²)	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
Medications:			
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

Laboratory results:			
RRF (ml/min/1.73m²)[1]	5.5 (2.5-9.2)	3.6 (0.0-8.6)	0.501
eGFR CKD-EPI (mL/min/1.73m²)[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
Electrocardiogram:			
QRS duration (ms)	107 ± 25	137 ± 41	0.010
Corrected QT interval (ms)	421 ± 35	443 ± 50	0.100

[1]Measured 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 arrhythmia.
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 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/m²)	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/m²)	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.

Figure 1

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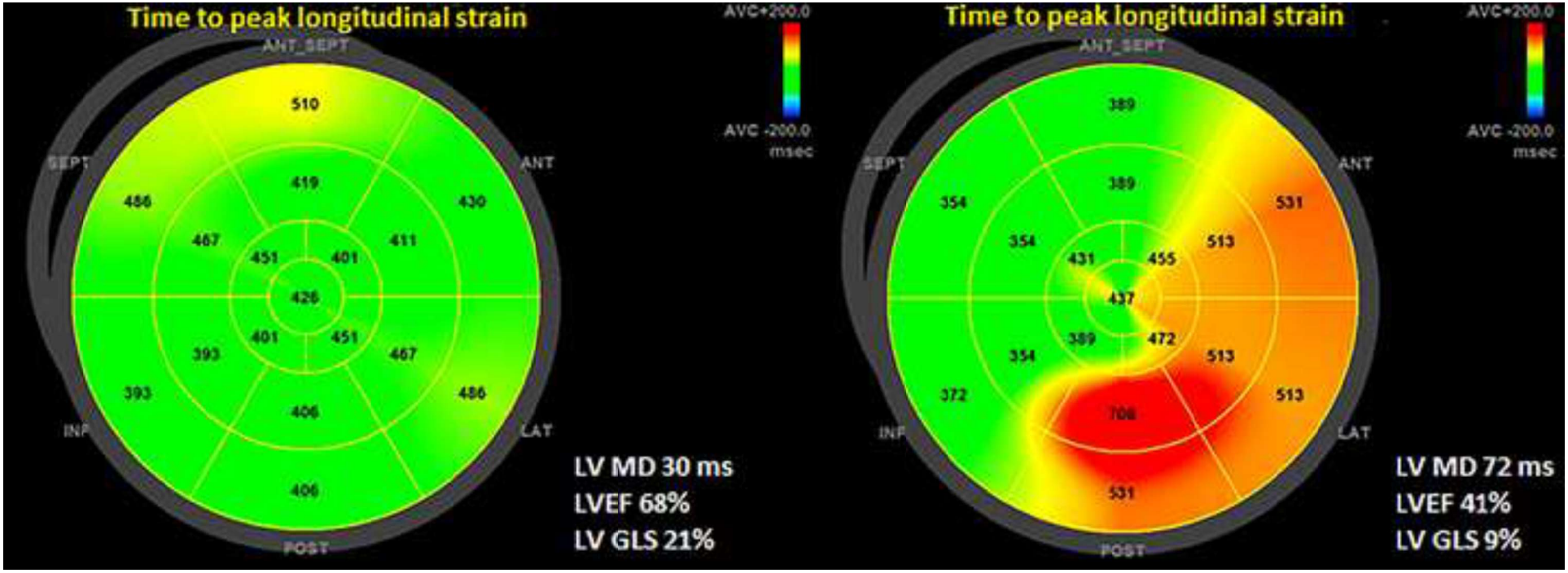

Figure 2

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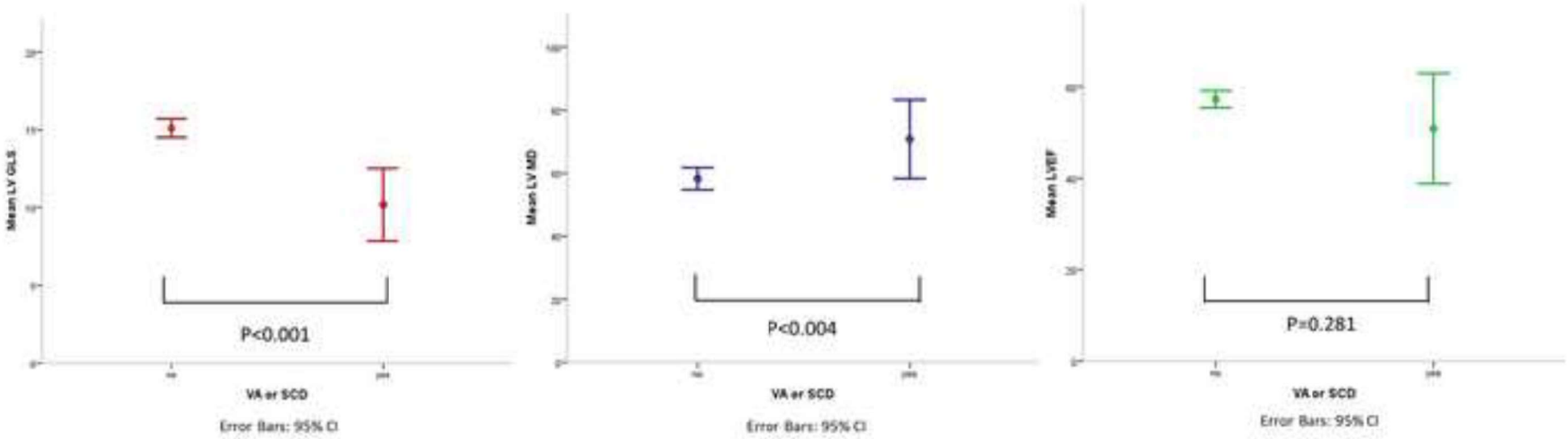

Figure 3
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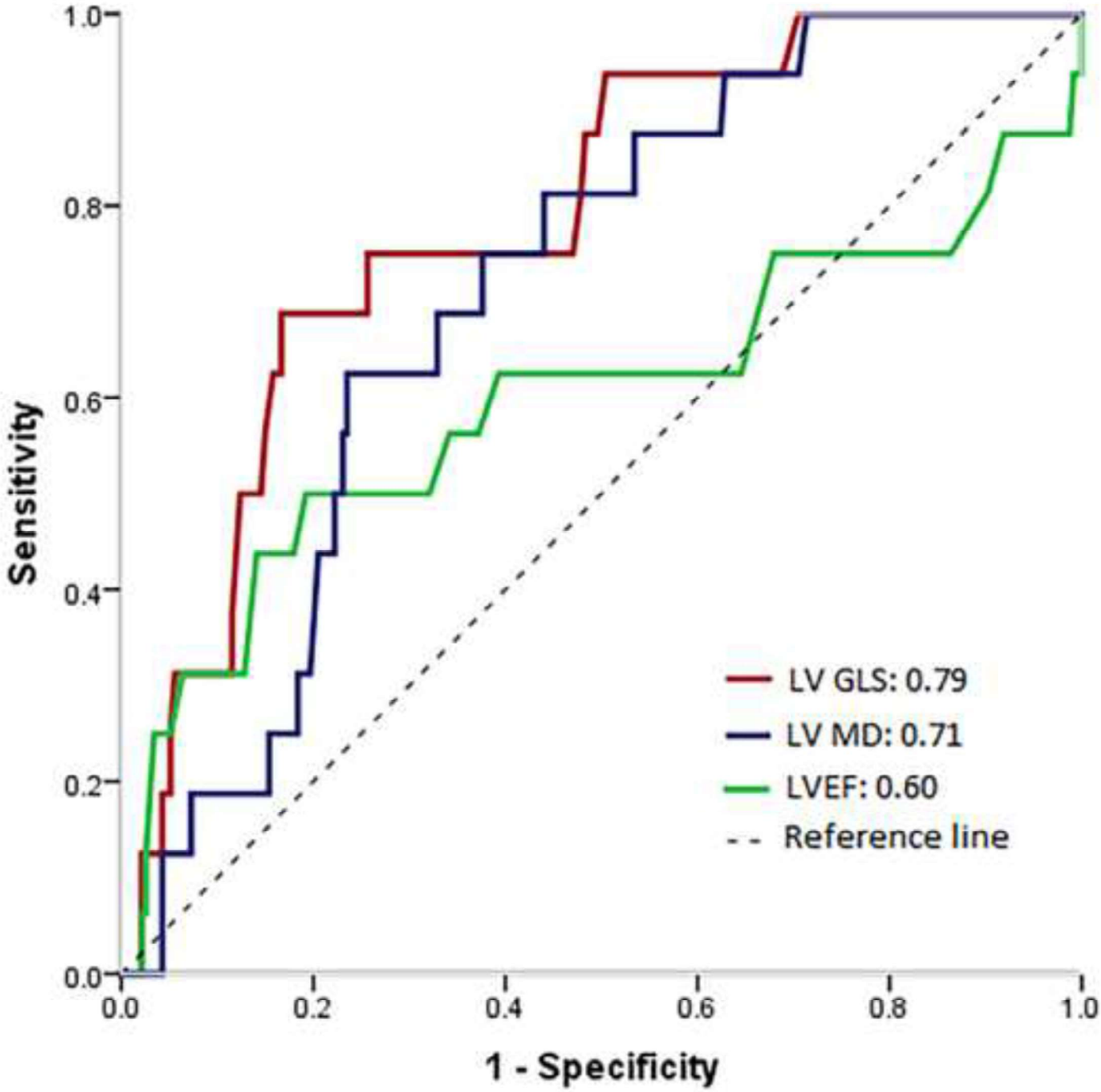

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