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Cardiovascular

Left atrial strain is associated with adverse cardiovascular events in patients with end-stage renal disease: Findings from the Cardiac, Endothelial Function and Arterial Stiffness in ESRD (CERES) study

Amrita Ayer[1] | **Upasana Banerjee**[1] | **Claire Mills**[2] | **Catherine Donovan**[2] | **Lauren Nelson**[3] | **Sanjiv J. Shah**[3] | **Ruth F. Dubin**[1]

[1]Division of Nephrology, San Francisco VA Medical Center/University of California, San Francisco, California, USA

[2]Center for Vascular Excellence, Division of Cardiology, San Francisco General Hospital/University of California, San Francisco, California, USA

[3]Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

Correspondence
Ruth F. Dubin, San Francisco VA Medical Center, 4150 Clement Street, Box 111A1, San Francisco, CA 94121, USA.
Email: ruth.dubin@ucsf.edu

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Abstract

Introduction: We lack cardiovascular (CV) markers for patients with end-stage renal disease (ESRD), and left atrial (LA) strain has not been studied definitively in this population. We examined associations of LA reservoir, conduit, and booster strain with major adverse cardiovascular events (MACE) among stable patients with ESRD on dialysis.

Methods: One hundred and ninety patients in the Cardiac, Endothelial and Arterial Stiffness in ESRD study underwent echocardiography, including strain imaging. The primary outcome was 2-year composite non-fatal MACE or CV death. We performed Cox proportional hazards regression for LA strain measures, adjusting for demographics, comorbidities, left ventricular global longitudinal strain (LV GLS), E/e' and LA volume index.

Findings: Mean ± SD LA reservoir strain was 24.1 ± 7.0%, and LA conduit strain 11.9 ± 5.1%. In age-adjusted analyses, lower LA reservoir strain and LA conduit strain were associated with the primary outcome (HR per 1-SD worsening LA strain parameter = 1.57 [95% CI 1.2–2.1], $p = 0.003$ and 1.68 [95% CI 1.2–2.3], $p = 0.002$, respectively). After adjusting for comorbidities, LA reservoir strain remained associated with the primary outcome and with deaths alone, and LA conduit strain with the primary outcome and hospitalizations alone ($p < 0.05$ for all). Associations of LA conduit strain were independent of LV GLS. Associations were stronger in participants with serum albumin <3.6 mg/dl (p for interaction 0.008).

Discussion: Left atrial reservoir strain and conduit strain were independently associated with MACE among patients with ESRD. Our study provides unique ascertainment of CV hospitalizations not attributed to missed dialysis, and LA conduit strain was a strong marker for this outcome.

KEYWORDS
chronic kidney disease, end-stage renal disease, left atrial function, strain imaging

INTRODUCTION

Patients with end-stage renal disease (ESRD) on dialysis have staggering rates of cardiovascular (CV) morbidity and mortality. Unfortunately, traditional CV disease risk factors often have "reverse" associations in patients with ESRD, including lipids[1] and blood pressure,[2] and we currently lack risk stratifying CV markers in this population. Indeed, the Kidney Disease Improving Global Outcomes recently cited the need for the development of ESRD-specific CV risk markers.[3]

Prior studies have demonstrated the utility of two echocardiographic parameters among patients with ESRD: E/e' and LV global longitudinal strain (GLS). E/e' is performed with tissue Doppler imaging, and elevated values of E/e' are indicative of increased LV filling pressure[4] and diastolic dysfunction.[5] Among patients with ESRD on dialysis, E/e' is associated with CV events and death.[6–8] Lower absolute values of LV GLS, a sensitive measure of LV systolic dysfunction (even in the presence of a normal LV ejection fraction), has been shown in several studies of ESRD patients to predict death[9–11] and HF hospitalizations.[12] In comparison, there are few studies of left atrial (LA) strain in the ESRD population. Left atrial strain is a metric of filling and emptying of the left atrium. Left atrial strain has been validated as a metric of diastolic dysfunction in both heart failure with reduced and preserved ejection fraction (HFrEF and HFpEF, respectively).[13] Lower values of LA strain (indicative of worse LA function) are predictive of adverse outcomes for individuals free of CV disease,[14,15] and patients with HFpEF.[16,17] Given that patients with ESRD often have diastolic dysfunction and are prone to HFpEF, LA strain could be a useful prognostic tool for these patients, but there are few studies of LA strain in this population.

There are three phases of LA function that can be measured on echocardiography using speckle-tracking analysis: reservoir strain, conduit strain, and booster (pump) strain. Table 1 explains the measurement of these three LA strain parameters along with E/e' and LV longitudinal strain in detail, along with their timing in the cardiac cycle and their clinical significance. We chose reservoir function as our primary predictor, since it has been validated in more studies than conduit or booster function.[18] Reservoir function represents LA filling from pulmonary venous return during LV systole.[18] The ability of the LA to fill is dependent on a low LA pressure and a compliant LA myocardium. Left atrial reservoir function is also influenced by LV systolic function, since descent of the LV base toward the LV apex determines descent of the mitral annulus and the degree of LA expansion during LV systole.[5] Conduit function, which follows reservoir function and represents LA passive emptying into the LV during early LV diastole, is dependent on the ability of the LV to relax quickly and a low LV pressure during early LV diastole. Left atrial booster function reflects the ability of the LA to actively empty into the LV during late LV diastole and is a measure of LA contraction. Normal LA booster strain is dependent on a vigorous LA contraction, a compliant LV at end-diastole, and a low LV end-diastolic pressure (LVEDP).[18]

We hypothesized that both LA reservoir and conduit strain would be prognostic metrics among patients with ESRD. Reservoir strain has predicted CVD outcomes in numerous populations.[18] We anticipated that conduit strain would also be a meaningful predictor of outcomes in the setting of ESRD. Patients with ESRD have significant LV hypertrophy, which is associated with impaired LV relaxation; therefore, we anticipated that LA conduit strain would be impaired (reduced) and would be associated with adverse outcomes in our study.

MATERIALS AND METHODS

Detailed methods for adjudication of CV outcomes, serum biomarkers and echocardiography, including reproducibility studies, are found in the Supporting Information (Methods).

Study participants

The *C*ardiac, *E*ndothelial Function and A*r*terial Stiffness in *ES*RD (CERES) study is a prospective observational study of 200 patients on hemodialysis or peritoneal dialysis, designed to provide comprehensive assessment of cardiac mechanics with modern echocardiographic measures, including speckle tracking echocardiography (STE), and to determine the utility of these measures for predicting CV outcomes. CERES participants were recruited from the UCSF Kidney Pancreas Transplant Clinic, the Zuckerberg San Francisco General (ZSFG) Hospital Chronic Dialysis Unit, and five Fresenius and DaVita dialysis units between February 2013 and April 2016. To be included, patients had to be on hemo- or peritoneal dialysis for at least 1 month. Any of the following led to exclusion: myocardial infarction (MI) in

TABLE 1 Definitions of echocardiographic parameters

Echocardiographic parameter	Definition	Concurrent with LV cardiac phase	Clinical significance
E/e'	E = velocity of blood passing through the mitral valve in early LV diastole (during the passive emptying of the LA into the LV in early LV diastole) e' = tissue velocity of the mitral annulus in early LV diastole, averaged between septal and lateral mitral annulus; reflects the ability of the LV to relax in early diastole	Early LV diastole	Higher values of E/e' are indicative of higher LV filling pressures and worse LV diastolic function
LA reservoir strain	LA peak positive longitudinal strain + LA peak negative longitudinal strain. Reflects the ability of the LA to expand and fill from the pulmonary veins during LV systole	LV systole	Lower values of LA reservoir strain are indicative of elevated LA pressure and/or a stiff, non-compliant LA
LA conduit strain	LA peak positive longitudinal strain. Reflects the ability of the LA to passively empty into the LV during early LV diastole	Early LV diastole	Lower values of LA conduit strain are indicative of impaired LV relaxation and/or elevated LV pressure in early diastole
LA booster strain	LA peak negative longitudinal strain. Reflects the ability of the LA to contract during late LV diastole	Late LV diastole	Lower values of LA booster strain are indicative of a stiff, non-compliant LV; elevated LV end-diastolic pressure; and/or reduced LA contractile function
LV global longitudinal strain	LV peak longitudinal strain. Reflects the ability of the LV to contract in the longitudinal direction, which is dependent on the health of the LV subendocardium. The subendocardium is susceptible to ischemia due to reduced coronary microvascular blood flow (coronary microvascular dysfunction) which can be caused by LV hypertrophy, LV fibrosis, or coronary endothelial dysfunction. Abnormal LV global longitudinal strain is also reflective of impaired cardiomyocyte function in the subendocardium	LV systole	Lower absolute values of LV global longitudinal strain are indicative of worse LV systolic function, even in the setting of normal LV ejection fraction (and therefore is a more sensitive marker of LV systolic dysfunction than LV ejection fraction)

Note: All strain values are presented as positive (absolute) values. Lower absolute values of each strain parameter are indicative of worse function.
Abbreviations: LA, left atrial; LV, left ventricular.

the prior 4 months, current infection, newly diagnosed or metastatic cancer or currently on chemotherapy, cocaine, or intravenous drug use in the last 6 months, or major surgery within the last month. Patients gave written informed consent, and the UCSF Committee for Human Research approved the study protocol. All procedures were in accordance with the Declaration of Helsinki.[19]

Study visits were held at the ZSFG Hospital Clinical Research Unit, and for patients on hemodialysis the visit was on the morning following the first hemodialysis session of the week. Left atrial reservoir and conduit strain are volume dependent, and there have been several studies that show LA reservoir and conduit strain decrease after fluid removal during hemodialysis.[20,21] For this reason, we evaluated strain parameters on the day after the

TABLE 2 Clinical characteristics by quartile of left atrial reservoir strain

Characteristic	Quartile 1 7.7%–18.9% (*N* = 47)	Quartile 2 18.9%–24.1% (*N* = 46)	Quartile 3 24.1%–28.8% (*N* = 47)	Quartile 4 28.8%–46.5% (*N* = 46)	*p*
Age (years)	58 (13)	60 (10)	56 (9.5)	48 (15)	<0.001
Female gender	17 (37)	17 (36)	12 (26)	18 (38)	0.59
Race					
White	12 (26)	13 (28)	15 (33)	10 (21)	0.73
Black	16 (35)	20 (43)	13 (28)	17 (36)	
Other	18 (39)	14 (30)	18 (39)	20 (43)	
Hispanic	7 (15)	11 (23)	16 (35)	17 (36)	0.076
Time on dialysis (months)	45 (23, 74)	47 (23, 94)	48 (17, 78)	37 (15, 72)	0.79
History of tobacco	30 (44)	18 (38)	27 (59)	23 (49)	0.24
Diabetes	28 (61)	24 (51)	19 (41)	15 (32)	0.033
MI	8 (17)	6 (13)	7 (15)	1 (2)	0.10
CVA	7 (15)	11 (23)	2 (4.4)	3 (6.4)	0.019
PAD	3 (6.5)	2 (4.3)	2 (4.4)	2 (4.3)	0.95
Heart failure	9 (19.6)	9 (19.2)	5 (11)	3 (6.4)	0.18
Peritoneal dialysis	2 (4.4)	5 (10.6)	4 (8.7)	6 (13)	0.54
Fistula or graft access	38 (83)	38 (81)	38 (83)	37 (79)	0.96
Cause of renal failure					
DM	17 (37)	14 (30)	15 (33)	11 (23)	0.66
HTN	13 (28)	15 (32)	11 (24)	10 (21)	
GN	3 (6.5)	1 (2)	2 (4.4)	4 (8.5)	
Other	13 (28)	17 (36)	18 (39)	22 (47)	
COPD or Asthma	7 (16)	6 (13)	7 (16)	3 (6.5)	0.51
Anuric	37 (80)	34 (72)	33 (73)	37 (79)	0.75
Beta blocker	25 (54)	32 (68)	26 (57)	29 (62)	0.54
ACEI or ARB	16 (35)	15 (32)	16 (35)	13 (28)	0.87
Statin	20 (51)	23 (51)	15 (39)	19 (42)	0.56
BMI	28 (4.6)	30 (6.2)	29 (7.2)	27 (7.9)	0.36
Weight over dry weight (kg)	0.5 (−0.3, 1.0)	0.3 (−0.1, 0.6)	0.4 (−0.3, 1.0)	0.4 (−0.1, 1.1)	0.97
SBP (mmHg)	139 (25)	135 (25)	137 (24)	129 (23)	0.20
DBP (mmHg)	76 (12)	72 (14)	76 (14)	73 (13)	0.34
Heart rate (beats)	71 (10)	69 (12)	71 (12)	69 (10)	0.69
Calcium (mg/dl)	8.8 (0.64)	8.8 (0.64)	8.8 (0.60)	9.1 (0.71)	0.14
Phosphorus (mg/dl)	4.7 (1.7)	4.6 (1.3)	4.7 (1.1)	4.9 (1.5)	0.73
PTH (pg/dl)	300 (170, 430)	270 (180, 440)	350 (212, 460)	304 (185, 430)	0.75
Albumin (g/dl)	3.5 (0.37)	3.6 (0.35)	3.6 (0.37)	3.8 (0.50)	0.005
Kt/V	1.6 (0.31)	1.6 (0.38)	1.5 (0.31)	1.6 (0.35)	0.17
Hemoglobin (g/dl) (at study visit)	11.3 (1.4)	11.4 (1.2)	11.5 (1.5)	11.2 (1.3)	0.95
Interleukin-6 (pg/ml)	7.2 (3.6, 12)	6.7 (4.8, 8.9)	5.1 (3.4, 8.4)	4.0 (2.2, 6.0)	0.035
C-reactive protein (mg/dl)	4.2 (2.0, 12)	5.2 (2.7, 12.5)	4.2 (1.8, 8.1)	3.0 (1.2, 4.7)	0.21
NT-proBNP (pg/ml)	14,500 (5800, 32,600)	4500 (2200, 9400)	5300 (1800, 13,000)	2240 (1200, 4500)	<0.001
Hs-TnT (pg/ml)	84 (51, 130)	87 (57, 108)	58 (40, 93)	41 (20, 69)	0.18

Note: Values are expressed as mean (SD) or median (IQR) or *n* (%). *p* value method: ANOVA (continuous variable) or chi-square (categorical variable).
Abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DBP, diastolic blood pressure; DM, diabetes mellitus; GN, glomerulonephritis; Hs–TnT, high sensitivity–troponin T; HTN, hypertension; MI, myocardial infarction; NT-proBNP, N-terminal pro B-type natriuretic peptide; PAD, peripheral arterial disease; PTH, parathormone; SBP, systolic blood pressure.

first dialysis session of the week. We did not evaluate the effect of hemodialysis on strain parameters. Additional details on study design and baseline variables are included in the Supporting Information.

CV outcomes

The primary outcome for this analysis was the composite of hospitalization for MACE and CV death. CV hospitalization alone or CV death alone were secondary outcomes. Hospitalizations for MACE were included in this analysis, if the primary diagnosis was MI, HF, percutaneous coronary intervention, coronary artery bypass graft (CABG), cerebral vascular accident (CVA), or arrhythmia. Hospital admissions for volume overload or electrolyte abnormality attributed primarily to missed dialysis session(s) were not considered MACE. Deaths were categorized as definitely CV (MI or HF leading to cardiogenic shock, CVA leading to brain death, or CV death asserted in the medical chart by a medical provider reviewing information from an outside hospital system), unknown cause (such as a patient found dead at home), or non-CV (such as sepsis and malignancy). We considered unknown deaths as probable CV deaths, given the high rates of sudden cardiac death among patients with ESRD, and we chose to include both definite CV deaths and unknown deaths in our analysis. Adjudications for CV outcomes are described in the Supporting Information.

Statistical analyses

First, we compared baseline characteristics among participants grouped by quartile of LA reservoir strain by ANOVA. We examined the distribution of LA measures and summarized all echocardiographic parameters among men and women. Each baseline characteristic or echocardiographic parameter was tested for its univariate association with the primary outcome using Cox regression. We calculated Spearman correlations between LA reservoir strain and other echocardiographic parameters. We visualized cut points for LA reservoir and LA conduit strain by plotted log of (time to event) for the primary outcome against LA measures, using polynomial regression. We confirmed cut points using receiver operator

TABLE 3 Echocardiographic parameters in women and men with ESRD

Echo parameter	All ($N = 189$)	Women $N = 65$	Men $N = 124$	p	HR (95% CI) for primary outcome	p
LV mass (g)	224 (66)	190 (47)	240 (69)	<0.001	1.08 (0.84, 1.40)	0.54
LV mass index (g/m2)	117 (31)	110 (25)	121 (32)	0.003	1.18 (0.93, 1.52)	0.18
MAC = moderate or severe	11 (6%)	4 (6%)	7 (6%)	0.89	1.1 (0.86, 1.3)	0.61
Afib rhythm = 1 (0 normal, 2 other)	1 (0.5%)	0 (0%)	1 (0.8%)	–	–	–
IVC collapsibility (%)	61 (9)	62 (10%)	60 (9%)	0.36	0.73 (0.55, 0.96)	0.027
Valvular disease, moderate (≥3)	27 (14%)	12 (19%)	15 (12%)	0.24	2.0 (1.05, 3.8)	0.036
PASP (mmHg)	34 (29, 43)	38 (11)	38 (14)	0.87	1.69 (1.36, 2.10)	<0.001
LVESV (ml)	44 (21)	35 (12)	49 (22)	<0.001	1.03 (0.81, 1.31)	0.82
LVEDV (ml)	107 (32)	86 (22)	118 (32)	<0.001	0.91 (0.71, 1.17)	0.47
Ejection fraction (%)	60 (8)	60 (6.4)	59 (8.7)	0.47	0.80 (0.63, 1.01)	0.064
LV global longitudinal strain (%)	17 (3.1)	17 (2.8)	16 (3.2)	0.36	0.59 (0.46, 0.77)	<0.001
E/A	1.0 (0.4)	1.0 (0.4)	1.0 (0.4)	0.68	0.90 (0.69, 1.19)	0.47
E/e'	13 (6.8)	15 (7.9)	12 (5.8)	0.008	1.36 (1.14, 1.62)	<0.001
Mitral deceleration (ms)	195 (47)	194 (53)	195 (44)	0.86	0.85 (0.65, 1.13)	0.27
LA volume (ml)	76 (24)	70 (20)	80 (25)	0.005	1.17 (0.94, 1.47)	0.16
LA volume index (ml/m^2)	40 (12)	38 (9.8)	40 (12)	0.29	1.27 (1.02, 1.58)	0.036
LA reservoir strain (%)	24 (7.0)	24 (6.6)	24 (7.1)	0.74	0.59 (0.45, 0.78)	<0.001
LA booster strain (%)	13 (4.5)	13 (5.2)	12 (4.1)	0.42	0.80 (0.60, 1.07)	0.13
LA conduit strain (%)	12 (5.1)	11 (4.9)	12 (5.1)	0.25	0.55 (0.40, 0.75)	<0.001

Note: LVEDV left ventricular end diastolic volume. Unadjusted HR are per SD of continuous echo variable.
Abbreviations: IVC, inferior vena cava; LVESV, left ventricular end systolic volume; MAC, mitral annular calcification; PASP, pulmonary artery systolic pressure.

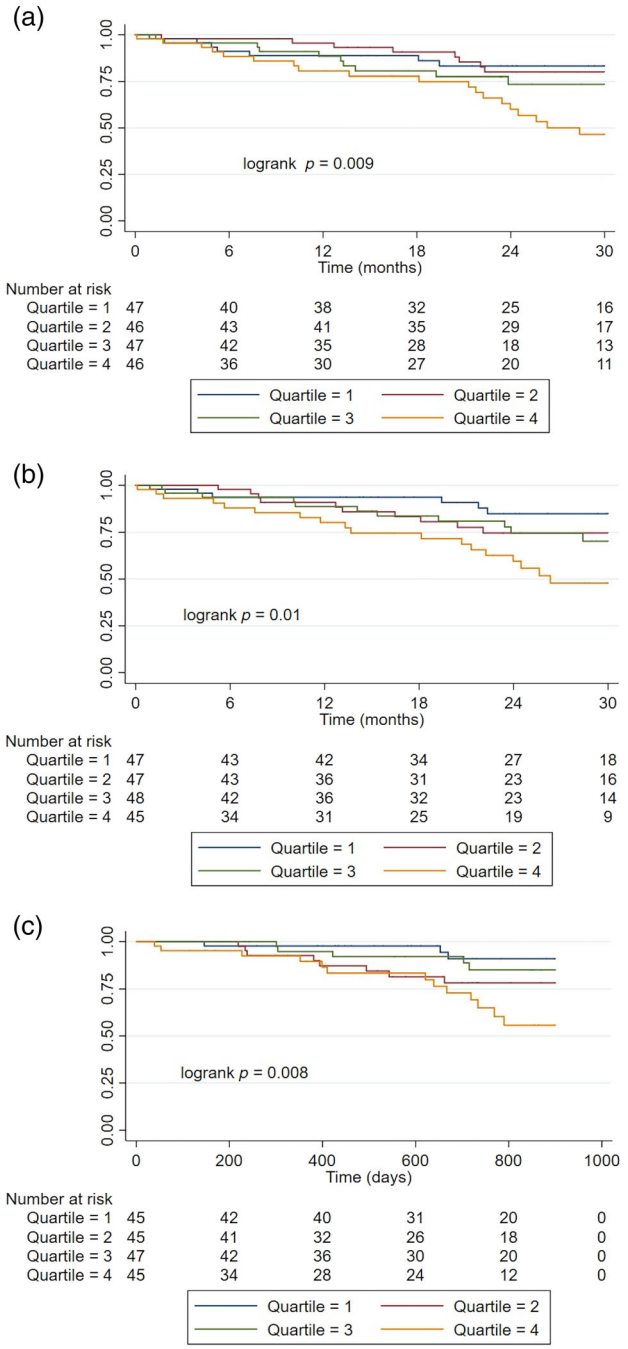

FIGURE 1 (a) Kaplan–Meier survival estimates for quartiles of left atrial (LA) reservoir strain and the primary outcome are shown over 2.5 years of follow-up (hospitalizations and deaths). (b) Kaplan–Meier survival estimates for quartiles of LA conduit strain and the primary outcome are shown over 2.5 years of follow-up (hospitalizations and deaths). (c) Kaplan–Meier survival estimates for quartiles of LA conduit strain and the secondary outcome (hospitalization alone) are shown over 2.5 years of follow-up (hospitalization alone) [Color figure can be viewed at wileyonlinelibrary.com]

curves, from which we also calculated sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Multivariable Cox regression was performed for LA parameters for primary and secondary outcomes. Model 1 adjusted for age only. Model 2 adjusted for demographics and comorbidities associated with the primary outcome at $p < 0.2$ (age, gender, history of tobacco, diabetes, chronic obstructive pulmonary disease or asthma, MI, CVA, peripheral artery disease, HF, systolic blood pressure, diastolic blood pressure) and factors known to associate with CV outcomes in ESRD cohorts (race,[22] time since dialysis initiation,[23] anuria[24]). Models 3–5 adjusted for LV GLS alone, E/e' alone, or LA volume index (LAVI) alone, respectively. We analyzed subgroups distinguished by age, gender, prevalent CV disease, time since dialysis initiation, serum albumin and LV ejection fraction, and reported interactions for these clinical factors as significant if $p < 0.1$. All statistical analyses were performed with STATA 14.0 (College Station, TX).

RESULTS

Demographic and baseline clinical characteristics for 189 CERES participants with LA strain measures are displayed in Table 2. The mean ± SD age among participants was 56 ± 13 years, 34% were women and 71% were non-White race. Eighty-one percent of patients were on hemodialysis (as opposed to peritoneal dialysis), with a median (IQR) time on dialysis of 45 (19, 79) months. The shortest time since dialysis initiation was 2 months. Diabetes and hypertension were the most common causes of ESRD. Older age, diabetes, history of stroke, lower albumin, higher IL-6 and higher NT-proBNP were more common in patients with lower (worse) LA reservoir strain. We found similar strain values in patients on hemodialysis and peritoneal dialysis. Mean (SD) LA reservoir strain was 23.8% (7.1) for hemodialysis, versus 26.2% (5.4) for peritoneal dialysis. Mean (SD) LA conduit strain was 11.5% (5.2) for hemodialysis, versus 11.9% (4.3) for peritoneal dialysis ($p > 0.1$ for both). Univariate associations for each baseline characteristic with the outcome are shown in Table S1.

The median (IQR) follow-up time was 24 months (13.3, 33.3 months). Thirty-five participants (19%) had hospitalizations for MACE, 31 (16%) died of definite or probable CV deaths, and 59 (31%) experienced the composite primary outcome of hospitalization for MACE, definite CV death, or probable CV death. There were 35 hospitalizations for MACE, including 12 MI, 7 definite HF, 4 probable HF, 8 arrhythmia, 2 CABG, and 2 CVA. Of the 31 deaths, 9 were definite and 22 were probable CV death. During 2 years of follow-up 37 patients were lost to follow up and 19 underwent kidney transplantation.

Echocardiographic parameters for men and women are displayed in Table 3. Men had higher LV mass index (LVMI), LV end-systolic volume, LV end-diastolic

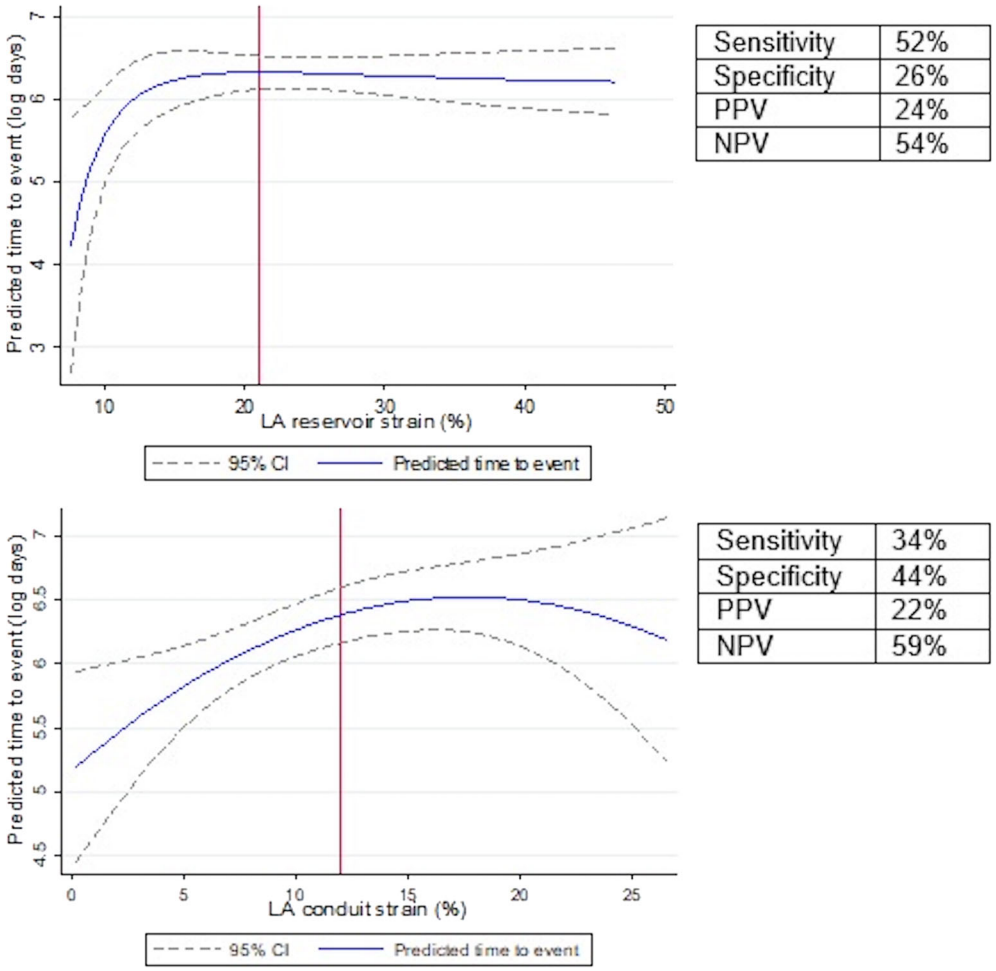

FIGURE 2 Cut points for left atrial (LA) reservoir strain and conduit strain for the primary outcome were visualized graphically. Cut points were 21% for LA reservoir strain, and 12% for LA conduit strain. NPV, negative predictive value; PPV, predictive value [Color figure can be viewed at wileyonlinelibrary.com]

volume. Women had higher E/e'. The distributions of both LA reservoir strain and LA conduit strain were parametric (Figure S1). Pulmonary artery systolic pressure (PASP), LV GLS, E/e', LA reservoir strain, and LA conduit strain were all associated with the primary outcome at $p < 0.001$; LA volume index was associated with the primary outcome at $p < 0.05$. Left atrial reservoir strain correlated with multiple echocardiographic parameters: LVMI, IVC collapsibility, LVESV, EF, E/A (all $p < 0.01$), and PASP, LV GLS, E/e', mitral deceleration, LA booster strain, LA conduit strain (all $p < 0.001$) (Table S2).

Kaplan–Meier curves for quartiles of LA reservoir strain showed graded associations with the primary outcome (log-rank $p = 0.009$) (Figure 1a) and secondary outcomes (both CV hospitalizations alone and CV death alone (log-rank $p < 0.05$ for both). Quartiles of LA conduit strain had graded associations with both the primary outcome (log-rank $p = 0.01$) (Figure 1b) and CV hospitalizations alone (log-rank $p = 0.008$) (Figure 1c). For the primary outcome, Q4/Q1 HR (95% CI) of LA reservoir was 3.5 (1.6–7.8), and for conduit strain was 4.6 (1.9–10.8). Left atrial volume index was not additive with either strain measure: HR (95%) for worst quartile LA reservoir strain and LAVI was 2.3 (1.2–4.5); for worst quartile LA conduit strain and LAVI, HR (95% CI) was 2.8 (1.4–5.6). Cut points for LA reservoir strain and LA conduit strain were <21%, and <12%, respectively. (Figure 2). The sensitivity and specificity for LA reservoir strain were calculated to be 52% and 26%, respectively and for LA conduit strain were 34% and 44%, respectively.

The association of LA reservoir strain with the primary outcome remained significant after adjustment for demographics and comorbidities and was independent of E/e' and LAVI, but fell short of independence of LV GLS ($p = 0.059$). Left atrial conduit strain had strong, independent associations with the primary outcome and with CV hospitalizations alone; its association with CV hospitalizations remained significant in all adjusted models (Table 4). Left atrial booster strain was associated with death alone, but not with the primary outcome or CV hospitalizations. (Table S3).

We tested the age-adjusted associations of LA reservoir and LA conduit strain for interactions by age (56 years), gender, prevalent CV disease, median time from dialysis initiation (44 months), median serum albumin (3.6 g/dl), and ejection fraction <45% (Figure 3).

TABLE 4 Associations of left atrial measures with cardiovascular outcomes

			No adjustment	Model 1	Model 2	Model 3	Model 4	Model 5
				Age	Age + demographics, comorbidities	LV global longitudinal strain	E/e'	LA volume index
	Outcome	*N* (events)	HR (95% CI), *p*-value					
LA volume index	Hospitalizations and deaths	188 (58)	1.26 (1.02, 1.57)	1.23 (0.99, 1.53)	1.19 (0.92, 1.5)	1.1 (0.89, 1.47)	1.13 (0.89, 1.4)	–
			0.036	0.058	0.18	0.30	0.30	
	Hospitalizations	183 (34)	1.1 (0.82, 1.5)	1.1 (0.81, 1.49)	1.04 (0.73, 1.5)	0.91 (0.64, 1.3)	0.99 (0.72, 1.4)	–
			0.51	0.56	0.844	0.62	0.99	
	Deaths	185 (31)	1.26 (0.94, 1.7)	1.20 (0.89, 1.62)	1.26 (0.88, 1.8)	1.24 (0.90, 1.7)	1.12 (0.81, 1.54)	–
			0.13	0.22	0.20	0.19	0.48	
LA reservoir strain	Hospitalizations and deaths	186 (58)	1.69 (1.3, 2.2)	1.57 (1.2, 2.1)	1.45 (1.1, 2.0)	1.40 (0.99, 2.0)	1.56 (1.1, 2.1)	1.68 (1.2, 2.3)
			<0.001	0.003	0.023	0.059	0.007	0.002
	Hospitalizations	181 (35)	1.63 (1.1, 2.3)	1.56 (1.1, 2.3)	1.43 (0.95, 2.1)	1.20 (0.76, 1.9)	1.44 (0.96, 2.1)	1.77 (1.2, 2.7)
			0.007	0.022	0.087	0.425	0.077	0.009
	Deaths	183 (30)	1.76 (1.2, 2.6)	1.58 (1.1, 2.4)	1.70 (1.0, 2.8)	1.51 (0.93, 2.5)	1.78 (1.1, 2.9)	1.81 (1.2, 2.8)
			0.004	0.027	0.035	0.097	0.019	0.01
LA conduit strain	Hospitalizations and deaths	187 (59)	1.79 (1.3, 2.4)	1.68 (1.2, 2.3)	1.5 (1.1, 2.1)	1.6 (1.1, 2.3)	1.6 (1.2, 2.2)	1.7 (1.3, 2.4)
			<0.001	0.002	0.025	0.009	0.003	0.001
	Hospitalizations	182 (35)	1.95 (1.3, 2.9)	1.93 (1.3, 2.9)	1.63 (1.04, 2.6)	1.72 (1.1, 2.7)	1.74 (1.2, 2.6)	1.93 (1.3, 2.9)
			0.001	0.002	0.032	0.021	0.009	0.002
	Deaths	184 (31)	1.63 (1.07, 2.5)	1.4 (0.87, 2.3)	1.33 (0.79, 2.3)	1.33 (0.81, 2.2)	1.46 (0.93, 2.3)	1.58 (1.02, 2.4)
			0.023	0.16	0.29	0.27	0.10	0.039

Note: HR are per SD higher LAVI. HR are per SD lower LA reservoir strain or LA conduit strain. Model 2 is adjusted for age, gender, race, dialysis vintage, tobacco history, diabetes, COPD or asthma, atherosclerotic heart or vascular disease, heart failure, systolic blood pressure, diastolic blood pressure, anuria.

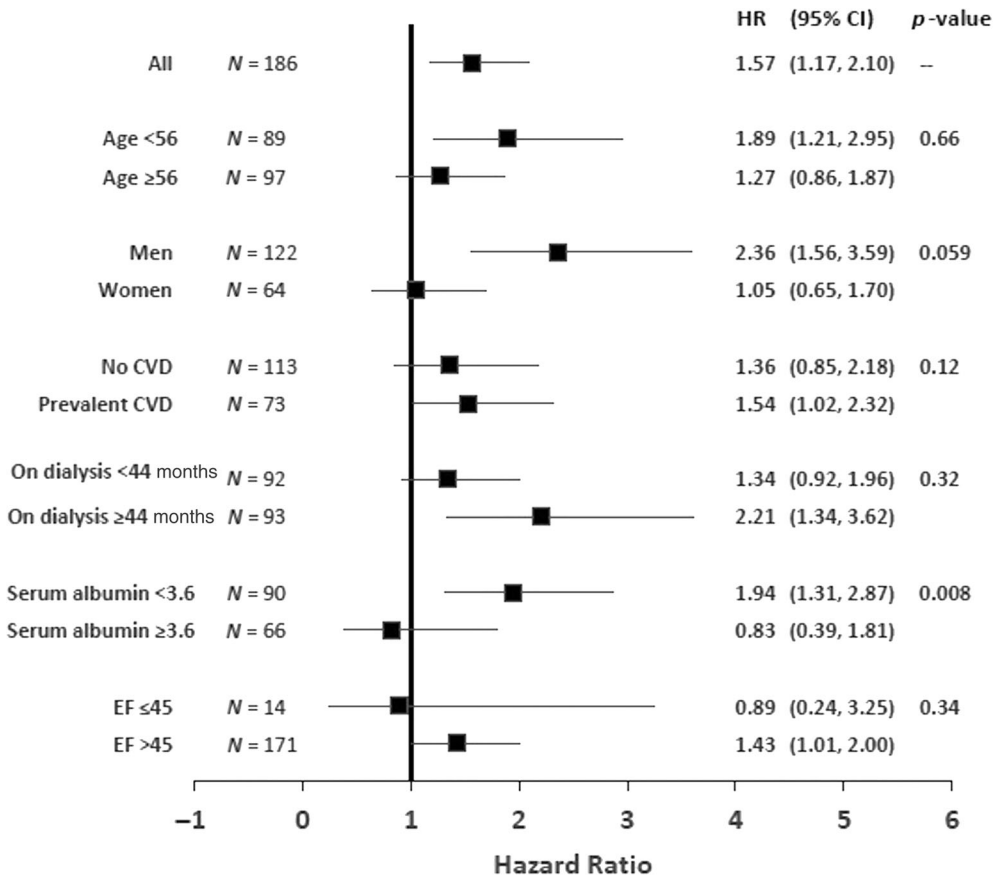

FIGURE 3 Subgroup analyses for the primary outcome showed that albumin, dichotomized as the median serum albumin (3.6 g/dl), was a significant interaction term for the association of left atrial (LA) reservoir strain with the primary outcome

Albumin was a significant interaction term for both reservoir and conduit strain, for primary outcome and death alone. For LA reservoir strain and death, albumin ≥3.6, HR (95% CI) per SD was 0.88 (0.21–3.71), versus 1.99 (1.15–3.43) for albumin <3.6 g/dl ($p = 0.008$). For LA conduit strain and primary outcome, albumin ≥3.6, HR (95% CI) per SD was 0.89 (0.32–2.5), versus 1.89 (1.26–2.80) for albumin <3.6 ($p = 0.009$). For LA conduit strain and death, albumin ≥3.6, HR (95% CI) was 0.99 (0.13–7.45) versus 1.58 (0.92–2.71) for albumin <3.6 ($p = 0.01$).

While the interaction with gender did not reach statistical significance, the association of LA reservoir strain with the primary outcome was markedly higher in men than in women (HR (95% CI) 2.36 (1.56, 3.59) versus 1.05 (0.65, 1.70), p for interaction = 0.059). A similar trend was noted for conduit strain: (HR (95% CI) for men: 2.1 (1.3, 3.3), for women: 1.37 (0.84, 2.23), p for interaction = 0.09). We are underpowered to compare patients on hemodialysis versus peritoneal dialysis, since only 17 patients were on peritoneal dialysis. However, we found little difference by dialysis type. For LA reservoir strain, age-adjusted HR (95% CI) for the composite outcome among hemodialysis patients was 1.59 (1.17, 2.16) compared to 3.9 (0.44, 34) among peritoneal dialysis patients (p for interaction = 0.44). For LA conduit strain, age-adjusted HR (95% CI) for the composite outcome among hemodialysis patients was 1.49 (1.04, 2.2), compared to 5.5 (1.04, 30) among peritoneal patients (p for interaction = 0.15).

DISCUSSION

In our study of LA strain measures in a well-phenotyped ESRD cohort with adjudicated MACE, we found that LA reservoir strain and conduit strain had stronger associations with MACE than LA volume index. Associations of LA reservoir strain were strongest for the primary outcome and CV death alone, independently of comorbidities, E/e' and LA volume index. Left atrial conduit strain was associated with the primary outcome and CV hospitalizations alone, independently of E/e', LA volume index and LV GLS.

Left atrial reservoir and conduit strain have been examined in few studies of ESRD with adjudicated outcomes. Tsai et al. report that LA strain was associated with overall and CV mortality in unadjusted analyses.[25] Papadopoulos et al. demonstrated in 79 ESRD patients that LA reservoir strain predicted paroxysmal atrial fibrillation.[26] A recent study of patients with pre-dialysis chronic kidney disease (CKD) Stages 3/4 by Gan et al. showed that LA reservoir strain was a very good predictor

(AUC 0.84) for MACE and overall death, and its association with the composite outcome was significant after adjustment for comorbidities and echocardiographic parameters.[27] To our knowledge, we are the first to characterize LA volume, LA reservoir strain, LA conduit strain, and LA booster strain in an ESRD cohort with adjudicated MACE. Average LA reservoir strain (24 ± 7%) was markedly worse than normal LA reservoir strain (>39%) described in a meta-analysis of healthy populations,[18] but similar to HFpEF patients in Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT),[17] and similar to patients with CKD.[27] The correlation we observed between lower (worse) LA strain with older age has also been found in healthy populations.[28–30] The correlation between worse (lower) LA strain and higher NT-proBNP has been noted previously in patients with a variety of CV diseases[31] and in patients with HFpEF.[17] In the normal state, BNP is primarily released by the LV myocardium whereas atrial natriuretic peptide is released by the LA myocardium; however, in the setting of HF, volume overload, or atrial fibrillation, the primary source of BNP (and therefore NT-proBNP) is the LA myocardium. In our study, clinical correlates of worse LA strain also included lower albumin and higher IL-6. It is interesting that the cut point of LA reservoir strain (<21%) found in our study to predict the primary outcome is the same as the cut point of <20.9% found to define severe diastolic dysfunction among HFpEF patients in the Soluble Guanylate Cyclase Stimulator in Heart Failure Patients (SOCRATES) trial.[13]

In our study, adjusting for LV GLS attenuated the associations of LA reservoir strain for primary and secondary outcomes but did not affect the associations of LA conduit strain with the primary outcome and with CV hospitalizations. Freed et al., in a cohort of patients with HFpEF, performed at the same Northwestern University Echocardiography Core Laboratory with the same imaging protocols as our study, found that LA reservoir strain was associated with a composite outcome of hospitalizations and death, independent of comorbidities and echocardiographic parameters, but associations of conduit strain were not significant after adjustment for echocardiographic parameters.[16] It is remarkable that in our study, LA conduit strain was associated with CV hospitalizations independently of comorbidities and echocardiographic parameters, including LV GLS. While our results would need replication in larger cohorts, it is possible that LA conduit strain could prove to be more useful in the ESRD population for risk stratification than in non-ESRD populations.

Associations of LA reservoir and conduit strain with the primary outcome and with CV death alone were stronger in patients with serum albumin below the median (3.6 g/dl), all at $p < 0.05$. Low albumin is a well-established marker of poor survival in ESRD, likely representing overall inflammation as well as malnutrition.[32,33] Patients with ESRD have heightened inflammation[34] that leads not only to accelerated atherosclerosis, but also to malnutrition and protein energy wasting[35] (clinically manifest as sarcopenia and frailty).[36] In our study, low albumin and high IL-6 were more common in those with worse LA reservoir strain, and both albumin and IL-6 had associations with the primary outcome in univariate analysis. In general, inflammation causes endothelial dysfunction[37] and atherosclerosis.[38] Correlations between higher LVEDP and CRP have been observed previously,[39] and higher LVEDP is related to LA pressure and function. It is unclear how inflammation could directly influence LA strain or whether there may be confounders causing high inflammation and impaired LA strain in parallel. While the mechanism may not be known, our data would support design of future studies that focus on patients with high levels of inflammatory markers, to validate these findings and target therapies to these individuals. If a study is planned for an intervention to improve LA strain, for example, one could preferentially recruit patients with reduced LA strain and increased inflammation in anticipation that these patients might be most likely to show benefit.

In our analyses, there was a trend for stronger associations with the outcome among men for both LA reservoir strain and LA conduit strain. There is precedent for gender differences in the prognostic utility of strain parameters. For example, in a healthy population, LV strain was more predictive of CV outcomes in men, but not in women.[40] Conversely, in one study, LA strain was a significant predictor of outcomes in women, but not men.[15] We acknowledge that there were fewer women than men in our study, and thus it is possible that we were underpowered to find predictive associations of strain parameters among women. It will be important in future CV studies in ESRD to recruit adequate numbers of women and to stratify analyses on gender.

Strengths and limitations

Unique features of our study include the consistent timing of echocardiography on the day after the first dialysis session of the week, a single sonographer who performed all the echocardiograms for the study, and the use of blinded echocardiography readings by a core laboratory. Another unique feature of our cohort is that MACE was adjudicated by direct chart review, excluding hospitalizations attributed to missing dialysis. These imaging and adjudication protocols likely contributed to the strong, independent associations of LA reservoir and conduit strain with CV outcomes. Our study has

limitations. As a single-center study, our sample size is modest, although this enabled us to have a single sonographer, likely resulting in more consistent imaging. Common to cohort studies of patients with ESRD, a number of participants were lost to follow-up or transplanted during the study period; however, the high rates of events gave us adequate power to find significant associations. We had only one patient with atrial fibrillation at baseline, and we did not follow patients for incident atrial fibrillation, so we could not study associations of LA strain measures with prevalent or incident atrial fibrillation. We had only one baseline visit with echocardiography, and thus we could not investigate whether LA strain is a precursor to worsening LV diastolic or systolic function. We were not able to collect complete information from the study participants' hemodialysis units, and thus the variables such as interdialytic weight gain could not be evaluated as potential confounders in our analysis. We had few patients on peritoneal dialysis, and generalizability of our results to patients on peritoneal dialysis would require further study.

CONCLUSIONS

In summary, to our knowledge, we present the first study showing that LA reservoir strain and conduit strain are independent markers of MACE in stable patients with ESRD on dialysis. Associations of LA reservoir strain were strongest for the primary outcome and CV death alone, while associations of LA conduit strain were strongest for the primary outcome and hospitalizations alone. Given the need for new CV markers and therapeutic targets for patients with ESRD, LA reservoir and conduit strain have the potential for high utility in this population.

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CONFLICT OF INTEREST

None to declare.

DISCLOSURES

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SUPPORTING INFORMATION

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