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ORIGINAL ARTICLE

Association of Left Atrial Function With Incident Chronic Kidney Disease in Older Adults

Wendy Wang, PhD, MPH; Jorge L. Reyes, MD, MS; Abayomi Oyenuga, MD, MPH; Anne A. Eaton, PhD, MS; Faye L. Norby, PhD, MPH; Romil Parikh, MBBS, MPH; Riccardo M. Inciardi, MD; Alvaro Alonso, MD, PhD; Pamela L. Lutsey, PhD, MPH; Charles A. Herzog, MD; Junichi Ishigami, MD, PhD; Kunihiro Matsushita, MD, PhD; Josef Coresh, MD, PhD; Amil M. Shah, MD; Scott D. Solomon, MD; and Lin Yee Chen, MD, MS

Abstract

Objective: To examine the association of left atrial (LA) function with incident chronic kidney disease (CKD) and assess the clinical utility of adding LA function to a CKD risk prediction equation.

Patients and Methods: We included 4002 Atherosclerosis Risk in Communities study participants without prevalent CKD (mean ± SD age, 75±5 years; 58% female, 18% Black). Left atrial function (reservoir, conduit, and contractile strain) was evaluated by 2D-echocardiograms on 2011 to 2013. Chronic kidney disease was defined as greater than 25% decline in estimated glomerular filtration rate of less than 60 mL/min/1.73 m^2, end-stage kidney disease, or hospital records. Cox proportional hazards models were used. Risk prediction and decision curve analyses evaluated 5-year CKD risk by diabetes status.

Results: Median follow-up was 7.2 years, and 598 participants developed incident CKD. Incidence rate for CKD was 2.29 per 100 person-years. After multivariable adjustments, the lowest quintile of LA reservoir, conduit, and contractile strain (vs highest quintile) had a higher risk of CKD (hazard ratios [95% CIs]: 1.94 [1.42-2.64], 1.62 [1.19-2.20], and 1.49 [1.12-1.99]). Adding LA reservoir strain to the CKD risk prediction equation variables increased the C-index by 0.026 (95% CI: 0.005-0.051) and 0.031 (95% CI: 0.006-0.058) in participants without and with diabetes, respectively. Decision curve analysis found the model with LA reservoir strain had a higher net benefit than the model with CKD risk prediction equation variables alone.

Conclusion: Lower LA function is independently associated with incident CKD. Adding LA function to the CKD risk prediction enhances prediction and yields a higher clinical net benefit. These findings suggest that impaired LA function may be a novel risk factor for CKD.

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Chronic kidney disease (CKD) is a progressive condition and a strong risk factor for cardiovascular disease.[1] Current literature indicates a highly interdependent relationship between the heart and the kidney, known as cardiorenal syndrome. The spectrum of disorders that are part of the cardiorenal syndrome demonstrate how acute or chronic cardiac disease can lead to acute or chronic worsening kidney function and vice versa.[2]

Greater left ventricular (LV) mass, lower LV ejection fraction, and greater left atrial (LA) volume index have been associated with incident CKD.[3,4] Furthermore, among patients with CKD, elevated E/e' is associated with an increased risk for kidney events.[5] However, little is known about the relationship between

From the Division of Epidemiology and Community Health, University of Minnesota, Minneapolis (W.W., F.L.N., R.P., P.L.L.); Lillehei Heart Institute and Department of Medicine (Cardiovascular Division), University of Minnesota

Affiliations continued at the end of this article.

LA function—a relatively novel and increasingly important prognostic biomarker[6,7]—and CKD.

Atrial myopathy is defined as abnormalities in LA structure and function. Recent evidence suggests impaired LA function precedes LA structural changes and may indicate a more advanced state of LA remodeling.[8] Lower (worse) LA function has been associated with an increased risk for cardiovascular events, independent of LA size.[6,9-12] In patients with CKD, impaired LA function has been associated with end-stage kidney disease and major cardiovascular events.[13,14] However, the relationship between LA function and incident CKD among those free of prevalent CKD is unknown.

As the burden of CKD continues to increase,[15] identifying those at a high risk for CKD is of paramount importance. Chronic kidney disease risk prediction models have been reported.[16-18] Given that echocardiographic measures of cardiac structure and function are associated with incident CKD,[3,4] they may aid in CKD risk prediction. Therefore, using data from the Atherosclerosis Risk in Communities (ARIC) study, we assessed the prospective association of echocardiographic parameters of LA function with incident CKD among participants free of baseline CKD. Furthermore, we evaluated whether the addition of LA function measures would improve CKD risk prediction and assessed clinical utility using decision curve analysis.

PATIENTS AND METHODS

Study Population

The ARIC study is a community-based cohort of predominantly Black and White adults. At baseline (1987 to 1989), 15,792 participants were recruited from 4 US communities: Forsyth County, North Carolina; Jackson, Mississippi; Washington County, Maryland; and suburbs of Minneapolis, Minnesota.[19] Since then, participants have attended several additional follow-up visits and are followed continuously for hospitalizations.

For this analysis, baseline was visit 5 (2011 to 2013) because echocardiograms were performed at this visit. We excluded those with suboptimal echocardiogram images for LA function measurements (ie, missing views, substantial foreshortening of the left atrium, or >2 segments could not be tracked), prevalent CKD (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2), missing covariates, and races other than Black or White and non-White individuals in the Minneapolis and Washington County centers due to small numbers. After exclusions, 4002 participants were included (Supplemental Figure 1, available online at http://www.mcpiqojournal.org).

Institutional review boards at each study center approved the study. All participants provided written informed consent.

Exposure Measurements

Left atrial function measures (LA reservoir, conduit, and contractile strain) were obtained from 2D-echocardiograms.[20] In brief, trained sonographers performed echocardiograms using Philips iE33 ultrasound systems with Vision 2011 software. Speckle-tracking vendor-dependent software using R-R gating with an autostrain algorithm (QLAB Advanced Quantification software 13.0; Philips Ultrasound) was used to measure LA function. Speckles were tracked frame by frame during a cardiac cycle in the apical 4-chamber view. In a random sample of 40 participants, the intraclass correlation coefficient for interreader and intrareader variability for LA reservoir strain were 0.91 and 0.98, respectively. For this analysis, the absolute values of LA conduit and contractile strain were used.

Outcome Ascertainment

Incident CKD was a composite of developing an eGFR of less than 60 mL/min/1.73 m^2 accompanied by at least a 25% decline from baseline, end-stage kidney disease identified through the US Renal Data System, or hospitalization or death with an International Classification of Diseases, ninth/tenth revision codes relevant to kidney disease in any position (Supplemental Table 1, available online at http://www.mcpiqojournal.org).[21] Estimated glomerular filtration rate was calculated using the CKD Epidemiology Collaboration equation based on creatinine.[22] Serum creatinine was measured using the Roche enzymatic method.

Covariate Measurements

Covariates obtained from visit 1 included ARIC field center, sex, race, birthdate, and education level, and other covariates were from visit 5. Participants self-reported their birthdate, sex, educational attainment, and smoking status. Age was calculated from participant's birthdate. Technicians recorded medication use from medication bottles that participants brought to study visits. Body mass index (calculated as the weight in kilograms divided by the height in meters squared) was derived from height and weight. Blood pressure was measured 3 times via a random-zero sphygmomanometer after a 5-minute rest and the final 2 measurements were averaged. Diabetes was defined as a fasting glucose of greater than or equal to 126 mg/dL, a nonfasting glucose of greater than or equal to 200 mg/dL, antidiabetic medication use in the past 2 weeks, or self-reported physician diabetes diagnosis. Coronary heart disease, heart failure, and stroke were adjudicated as previously defined.[23-25] Hemoglobin A1c (HbA1c) was measured from stored whole blood samples using high-performance liquid chromatography (Tosoh G7 analyzer; Tosoh Biosciences) standardized to the Diabetes Control and Complications Trial assay.[26,27] Urine albumin-to-creatinine ratio was calculated as the ratio of albumin-to-creatinine in a spot urine sample. Atrial fibrillation (AF) was ascertained from electrocardiograms (ECGs) obtained during study visits and hospital discharge records.[28] Additional AF cases were identified from an ambulatory ECG monitoring device that a subset of participants wore at visit 6 (2016-2017). Participants without a history of cardiac electronic device implant or a skin allergic reaction to adhesive tape were invited to wear the ambulatory ECG monitoring device for a prescribed wear time of 14 days.[29] Peripheral artery disease was defined by hospital admission for peripheral artery disease, leg amputation, or leg revascularization procedures identified using International Classification of Diseases codes.

Echocardiogram measures were obtained from 2D-echocardiograms at visit 5. Left ventricular ejection fraction was calculated as 100 × (LV end-diastolic volume − LV end-systolic volume)/LV end-diastolic volume. Peak lateral and septal mitral annular relaxation velocities (e') were assessed using tissue Doppler imaging. E/e' ratio was calculated as the E wave divided by e'.[20,30] Left ventricular mass index was calculated from LV linear measures and indexed to body surface area.[31] Left atrial size was measured at the end of systole using biplane disk summation and indexed to body surface area to derive LA volume index.[31]

Statistical Analyses

Baseline characteristics were described using means and SDs for continuous variables and frequencies and percentages for categorical variables. Cox proportional hazards models were used to assess the association of LA function with incident CKD. Left atrial function measures were assessed categorically as quintiles (highest quintile was the reference category) and continuously per 1-SD decrement. Follow-up time was defined as time from visit 5 to the occurrence of incident CKD, loss to follow-up, death, or December 31, 2019, whichever occurred first. Of note, participants from the Jackson center were followed through 2017 because data were only available through 2017. Multivariable models adjusted for sociodemographic characteristics, baseline eGFR, CKD risk factors, and echocardiogram measures. The proportional hazards assumption was evaluated by including an interaction term between each LA function measure and log(time) in the fully adjusted model. In the primary analysis, the proportional hazards assumption held for LA reservoir and contractile strain, but a minor deviation was noted for LA conduit strain (P=.02). Interactions by sex and race were assessed and considered present at P<.10.

Cumulative incidence curves and restricted cubic splines were constructed to display the fully adjusted relationship between LA function measures and CKD incidence. For the restricted cubic splines, 3-7 knots were assessed, and 3 knots were used because it had the lowest Akaike information criterion (AIC).

Several sensitivity analyses were performed. First, participants with diastolic dysfunction (E/e' > 14)[32] were excluded because LA remodeling can occur in those

with LV diastolic dysfunction. Second, we excluded participants with LA enlargement (LA volume index $\geq$ 34 mL/m^2).[31] Third, those with prevalent or incident AF were excluded. Fourth, participants taking angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers were excluded because these medications could affect creatinine clearance.[33] Fifth, we accounted for the competing risk of death using the Fine-Gray method. Sixth, multiple imputation by chain equation (MICE) was used to impute LA function data for participants who had an echocardiogram but were missing LA function data. For the MICE analysis, clinical characteristics and echocardiographic variables were used to create 10 data sets without missing values. SAS procedures proc MI and proc MIANALYZE were used.

Nelson et al[16] developed CKD risk prediction equations for participants with and without diabetes because some variables (eg, HbA1c) were differentially available based on diabetes status. Using the CKD risk prediction equation variables,[16] we assessed whether adding LA function measures could improve 5-year CKD risk prediction. Risk prediction and decision curve analyses were done separately for participants with and without diabetes at baseline. For participants without diabetes, variables included age, sex, race, eGFR, cardiovascular disease history (stroke, myocardial infarction, or heart failure), ever smoker, hypertension, body mass index, and albumin-to-creatinine ratio. For participants with diabetes, diabetes medication use, insulin use, and HbA1c were additionally included.[16] Risk prediction performance was assessed by evaluating model discrimination with Harrell C-index. Change in C-index (95% CI) was calculated by bootstrapping with 1000 iterations. AIC estimated model prediction error. To assess the clinical utility, decision curve analysis was performed to show the predicted clinical net benefit.[34] The predicted net benefit shows the net true-positive results. Analyses were conducted using SAS (v9.4; SAS Institute Inc.) and R (v4.2.1).

RESULTS

At visit 5, participants were aged (mean $\pm$ SD) 75$\pm$4.9 years, 58% were female, and 18% identified as Black individuals. Those who developed CKD were more likely to be older, identify as Black, have lower educational attainment, higher prevalence of cardiovascular disease and risk factors, lower eGFR, higher HbA1c, and more adverse LA and LV remodeling (Table 1). Participant characteristics stratified by LA function measures are presented in Supplemental Table 2 (available online at http://www.mcpiqojournal.org).

LA Function and CKD

Over a median follow-up of 7.2 years, there were 598 cases of incident CKD. Incidence rate for CKD was 2.29 per 100 person-years. The lowest quintile of each LA function measure had the highest cumulative incidence of CKD (Figure 1). Incidence rates for CKD were 4.57, 3.73, and 3.58 per 100 person-years for the lowest quintiles of LA reservoir, conduit, and contractile strain, respectively (Table 2). After full model adjustments, the lowest quintiles of all LA function measures were significantly associated with incident CKD when compared with their respective highest quintiles (hazard ratios [95% CIs] were 1.94 [1.42-2.64], 1.62 [1.19-2.20], and 1.49 [1.12-1.99] for LA reservoir, conduit, and contractile strain, respectively). Significant associations were also observed when LA function measures were assessed continuously per 1-SD decrement. There was no evidence of nonlinearity for any LA function measure (Supplemental Figure 2, available online at http://www.mcpiqojournal.org). Results stratified by sex and race found overall consistent results without significant interactions ($P_{\text{interaction}}$>.10) (Supplemental Tables 3 and 4, available online at http://www.mcpiqojournal.org).

Sensitivity Analyses

The following sensitivity analyses were performed: (1) excluded 563 participants with diastolic dysfunction (Supplemental Table 5, available online at http://www.mcpiqojournal.org); (2) excluded 538 participants with enlarged LA volume index (Supplemental Table 6, available online at http://www.mcpiqojournal.org); (3) excluded 801 participants who had prevalent or incident AF (Supplemental Table 7, available online at http://www.mcpiqojournal.org); (4) excluded 1715 participants who were taking ACE inhibitors or angiotensin II receptor blockers

TABLE 1. Baseline Participant Characteristics: The Atherosclerosis Risk in Communities Study, 2011-2013[a,b]

	Incident chronic kidney disease[c] (n=598)	No incident chronic kidney disease (n=3404)
Demographic characteristic		
Age (y)	75.5±5.0	74.7±4.8
Female sex	308 (51.5)	2005 (58.9)
Black race	112 (18.7)	589 (17.3)
Less than high school education	99 (16.6)	366 (10.8)
Smoking status		
Current smokers	41 (6.9)	214 (6.3)
Former smokers	314 (52.5)	1658 (48.7)
Never smokers	243 (40.6)	1532 (45.0)
Clinical characteristic		
Body mass index (kg/m^2)	29.6±5.7	28.1±5.3
Systolic blood pressure (mm Hg)	133.3±18.2	129.0±16.8
eGFR (mL/min/1.73m^2)	72.2±11.0	77.6±11.4
HbA1c (%)	6.2±1.1	5.8±0.7
Antihypertensive medication use	503 (84.1)	2280 (67.0)
Diabetes	270 (45.2)	867 (25.5)
Coronary heart disease	123 (20.6)	408 (12.0)
Heart failure	98 (16.4)	288 (8.5)
Stroke	36 (6.0)	76 (2.2)
Atrial fibrillation	67 (11.2)	235 (6.9)
Peripheral artery disease	26 (4.3)	102 (3.0)
Echocardiogram measures		
LA reservoir strain (%)	28.8±9.9	32.5±8.4
LA conduit strain (%)	13.2±5.2	15.1±5.7
LA contractile strain (%)	15.7±6.8	17.5±6.2
LA volume index (mL/m^2)	28.7±9.9	25.6±9.0
LV ejection fraction (%)	64.3±8.0	65.5±6.1
LV mass index (g/m^2)	87.6±24.0	77.4±18.2
E/e' average ratio	11.9±5.0	10.7±3.5

Continued on next column

TABLE 1. Continued

[a]Abbreviations: eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; LA, left atrial; LV, left ventricular.
[b]Data are expressed as mean ± SD or n (%).
[c]Incident chronic kidney disease was ascertained through 2019.

(Supplemental Table 8, available online at http://www.mcpiqojournal.org); (5) accounted for the competing risk of death (Supplemental Table 9, available online at http://www.mcpiqojournal.org); and (6) imputed missing LA function data using MICE (Supplemental Table 10, available online at http://www.mcpiqojournal.org). For all sensitivity analyses, results were similar to the primary analysis.

CKD Risk Prediction

Risk prediction performance was assessed after individually adding LA reservoir, conduit, and contractile strain to the CKD risk prediction equation variables[16] (Table 3). In participants without diabetes, the C-index was 0.763 (95% CI, 0.725-0.800) for the model with the CKD risk prediction equation variables. The addition of each LA function measure increased the C-index. The model that added LA reservoir strain increased the C-index the most (change in C-index, 0.026; 95% CI, 0.005-0.051) and had the lowest AIC. Among participants with diabetes, the C-index (95% CI) for the model with the CKD risk prediction equation variables was 0.701 (95% CI, 0.658-0.744). Of all LA function measures, the addition of LA reservoir strain increased the model discrimination the most (change in C-index, 0.031; 95% CI, 0.006-0.058) and had the lowest AIC.

When candidate variables were individually assessed for prediction of CKD (Supplemental Table 11, available online at http://www.mcpiqojournal.org), in participants without diabetes, eGFR had the highest

C-index of 0.682 (95% CI, 0.639-0.726), followed by LA reservoir strain (C-index, 0.678; 95% CI, 0.628-0.727). Among those with diabetes, LA reservoir strain had the highest C-index of 0.650 (95% CI, 0.604-0.697).

Decision Curve Analysis

Decision curves, stratified by diabetes status, are presented in Figure 2. Among participants without diabetes, the model that added LA reservoir strain had a higher net benefit than the model with the CKD risk prediction equation variables only over an absolute 5-year risk threshold of 1%-10% (Supplemental Table 12, available online at http://www.mcpiqojournal.org). At a 5-year risk threshold of 5%, there was a predicted net benefit of 2.95 per 100 participants in the model with LA reservoir strain, compared with 2.69 per 100 participants in the model with the CKD risk prediction equation variables. In participants with diabetes, the models that added LA reservoir and contractile strain had a higher net benefit than the model with the CKD risk prediction equation variables over an absolute 5-year risk threshold of 2%-10% (Supplemental Table 13, available online at http://www.mcpiqojournal.org); at an absolute 5-year risk threshold of 1%, all 3 models had equal net benefit. The predicted net benefit at a 5-year risk threshold of 5% was 9.36, 9.80, and 9.72, for the models with the CKD risk prediction equation variables, the addition of LA reservoir strain, and the addition of LA contractile strain, respectively.

DISCUSSION

In this analysis of a community-based cohort, lower LA function (LA reservoir, conduit, and contractile strain) was associated with a greater risk of CKD after adjustments for cardiovascular risk factors, baseline eGFR, and echocardiogram measures. Furthermore, the addition of LA function measures, particularly LA reservoir strain, to the CKD risk prediction equation variables improved risk prediction and yielded a higher predicted clinical net benefit. Overall, results from this analysis suggest that LA function is a novel and independent risk factor for CKD and could potentially aid in CKD risk prediction.

Previous studies have shown that adverse changes in cardiac structure and function are associated with a greater risk for incident CKD or a decline in kidney function.[3-5,13,35-39] However, several studies were comprised of selected study populations (eg, patients with CKD).[5,13,36-39] Moreover, among studies consisting of participants free of baseline CKD, LV measures or LA volumes were assessed,[3,4] but not LA function. Recently, cumulative evidence indicates that atrial myopathy is an independent risk factor for a broad range of adverse health outcomes, including cardiovascular events and dementia.[6,7,12,40] The novel findings of this study advance the field by demonstrating LA function as a potential risk factor for CKD—an increasingly important public health problem[15,41]—independent of established CKD risk factors, LA size, and LV measures.

Left atrial function measures may also have clinical utility in enhancing CKD risk prediction. After adding LA function measures to the CKD risk prediction equation developed by Nelson et al,[16] all 3 LA function measures increased the C-index, with LA reservoir strain increasing the C-index the most. Furthermore, decision curve analysis indicated that among participants with and without diabetes, the model that included LA reservoir strain had a higher net benefit than the model with the CKD risk prediction equation variables alone. As the public health burden of CKD continues to increase,[15] identifying patients at high risk for CKD so as to prevent CKD is of paramount importance. In addition to modifying lifestyle risk factors (eg, adhering to a healthy diet, not smoking, and being physically active)[42] to prevent CKD, pharmacologic agents, such as ACE inhibitors, finerenone, and sodium-glucose cotransporter-2 inhibitors, prevent kidney failure in people with CKD.[43-45]

Importantly, incorporating LA function into clinical CKD risk assessment would be readily implementable given that echocardiograms are widely available, and LA function can be measured offline from previously obtained echocardiograms using vendor-independent software. In our analysis, echocardiograms were obtained in 2011-2013, but LA function was not measured until 2019. Although there may be challenges in integrating LA function into routine clinical practice owing to the current lack of standardization across vendor software, efforts are being made to

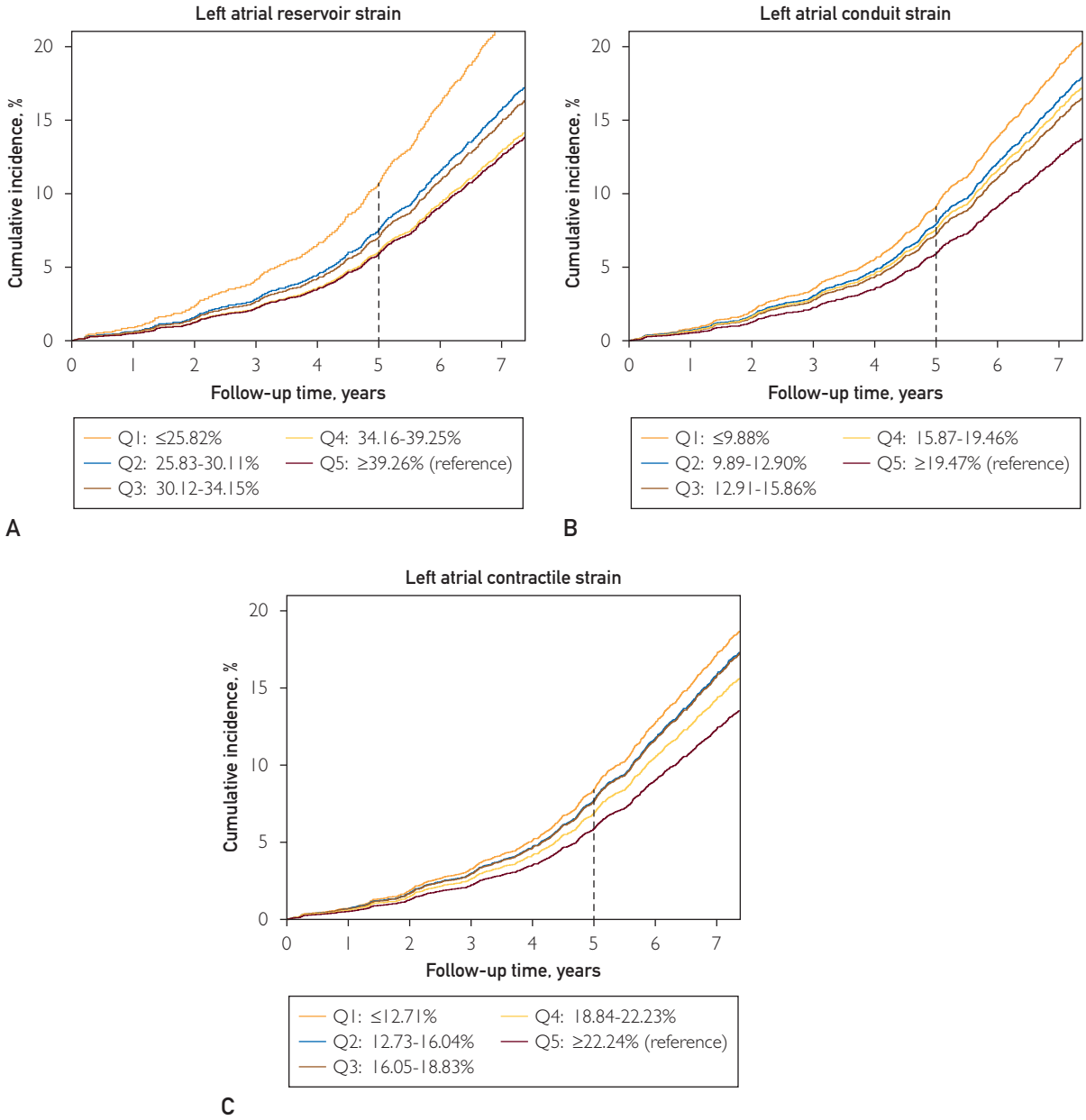

FIGURE 1. The cumulative incidence of chronic kidney disease by quintiles of left atrial reservoir, conduit, and contractile strain. At 5 years, the cumulative incidence of chronic kidney disease for each LA function quintile were as follows: LA reservoir strain (Q1: 10.78%; Q2: 7.57%; Q3: 7.12%; Q4: 6.09%; Q5: 5.93%); LA conduit strain (Q1: 9.22%; Q2: 8.01%; Q3: 7.30%; Q4: 7.66%; Q5: 5.97%); and LA contractile strain (Q1: 8.89%; Q2: 8.16%; Q3: 8.09%; Q4: 7.27%; Q5: 6.20%). Adjusted for age, sex, race/center, education, baseline eGFR, body mass index, smoking status, HbA1c, systolic blood pressure, diabetes, stroke, coronary heart disease, heart failure, atrial fibrillation, peripheral artery disease, antihypertensive medication use, LV ejection fraction, E/e' average ratio, LV mass index, LA volume index. eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; LA, left atrial; LV, left ventricular.

standardize LA function measurements[46] and manufacturers have begun to develop standardized software packages.[46,47]

The relationship between LA function and CKD may be due to several mechanisms. The LA is closely related to LV function and plays a

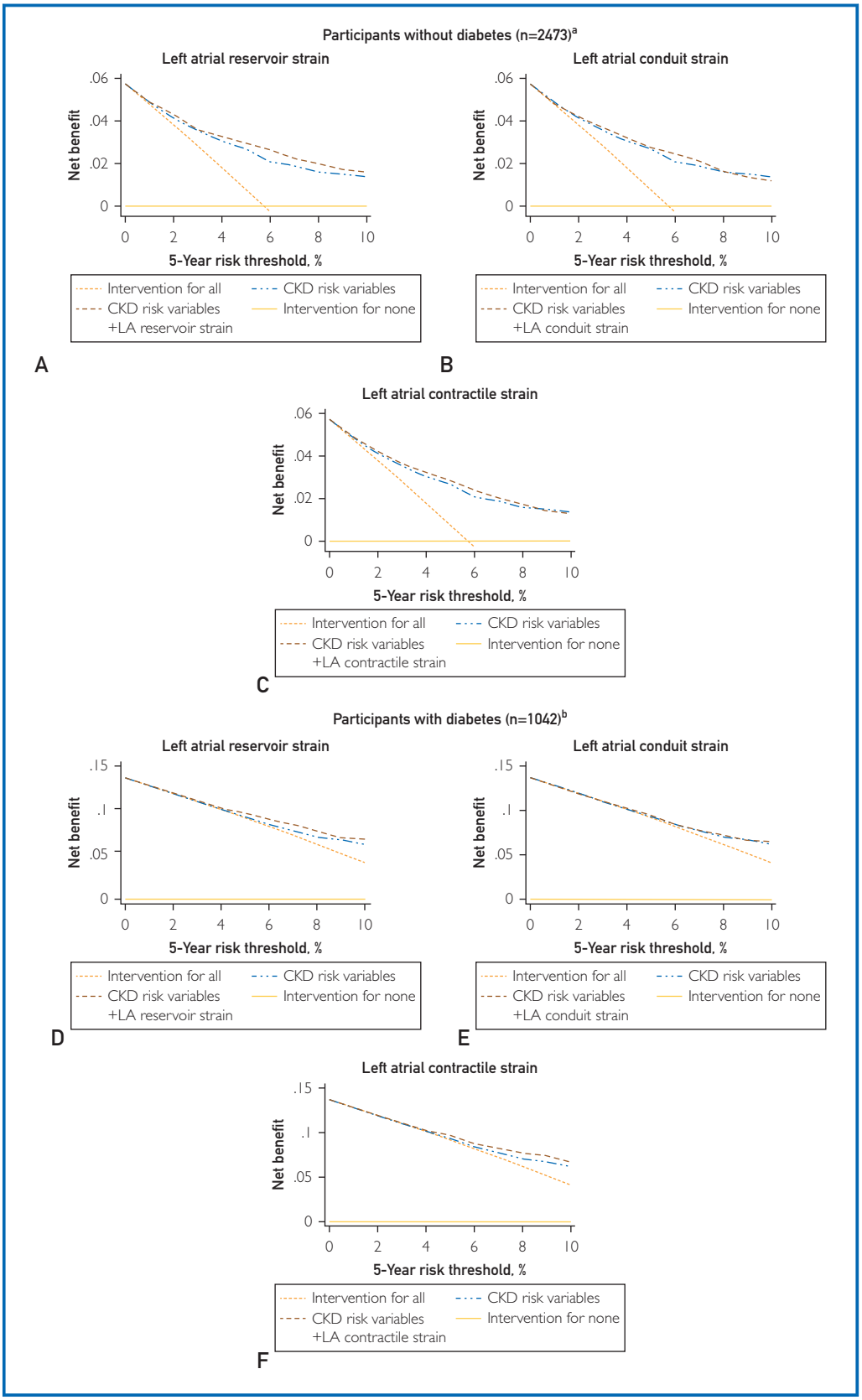

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TABLE 2. Association of Left Atrial Function Measures with Incident CKD: The Atherosclerosis Risk in Communities Study, 2011-2019 (n=4002)[a]

	LA reservoir strain (%)					
	≤25.82 (n=801)	25.83-30.11 (n=800)	30.12-34.15 (n=801)	34.16-39.25 (n=799)	≥39.26 (n=801)	Per 1-SD decrease (8.6)
N, incident CKD	200	125	107	89	77	598
IR per 100 PY	4.57	2.42	1.99	1.62	1.37	2.29
HR (95% CI)						
Model 1	3.50 (2.67-4.59)	1.75 (1.31-2.33)	1.42 (1.06-1.91)	1.23 (0.90-1.67)	Reference	1.59 (1.47-1.73)
Model 2	2.65 (1.99-3.54)	1.44 (1.08-1.92)	1.29 (0.96-1.73)	1.07 (0.79-1.46)	Reference	1.49 (1.35-1.64)
Model 3	1.94 (1.42-2.64)	1.31 (0.98-1.75)	1.22 (0.91-1.64)	1.03 (0.76-1.40)	Reference	1.29 (1.16-1.44)
	LA conduit strain (%)					
	≤9.88 (n=800)	9.89-12.90 (n=799)	12.91-15.86 (n=805)	15.87-19.46 (n=798)	≥19.47 (n=800)	Per 1-SD decrease (5.7)
N, incident CKD	174	135	113	105	71	598
IR per 100 PY	3.73	2.68	2.10	1.95	1.27	2.29
HR (95% CI)						
Model 1	2.94 (2.21-3.91)	1.99 (1.49-2.67)	1.62 (1.20-2.19)	1.54 (1.14-2.08)	Reference	1.44 (1.32-1.59)
Model 2	2.07 (1.54-2.77)	1.54 (1.15-2.07)	1.30 (0.96-1.75)	1.34 (0.99-1.82)	Reference	1.28 (1.16-1.41)
Model 3	1.62 (1.19-2.20)	1.38 (1.03-1.86)	1.25 (0.92-1.69)	1.32 (0.97-1.78)	Reference	1.15 (1.04-1.27)
	LA contractile strain (%)					
	≤12.72 (n=800)	12.73-16.04 (n=803)	16.05-18.83 (n=799)	18.84-22.23 (n=800)	≥22.24 (n=800)	Per 1-SD decrease (6.3)
N, incident CKD	168	124	114	104	99	598
IR per 100 PY	3.58	2.38	2.19	1.91	1.60	2.29
HR (95% CI)						
Model 1	2.27 (1.75-2.94)	1.55 (1.18-2.04)	1.45 (1.10-1.92)	1.23 (0.93-1.64)	Reference	1.35 (1.25-1.46)
Model 2	1.92 (1.47-2.52)	1.52 (1.15-2.01)	1.46 (1.11-1.94)	1.25 (0.94-1.66)	Reference	1.29 (1.18-1.41)
Model 3	1.49 (1.12-1.99)	1.36 (1.03-1.79)	1.34 (1.02-1.78)	1.19 (0.90-1.59)	Reference	1.17 (1.06-1.28)

[a]Abbreviations: CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; HR, hazard ratio; IR, incidence rate; LA, left atrial; LV, left ventricular; PY, person-year; SD, standard deviation.

Model 1: adjusted for age, sex, race/center, education, and baseline eGFR. Model 2: adjusted for model 1 plus body mass index, smoking status, HbA1c, systolic blood pressure, diabetes, stroke, coronary heart disease, heart failure, atrial fibrillation, peripheral artery disease, and antihypertensive medication use. Model 3: adjusted for model 2 plus LV ejection fraction, E/e' average ratio, LV mass index, and LA volume index.

vital role in LV filling.[8,48,49] Reduced LA function can influence LV filling, leading to a decrease in cardiac output.[49] Lower cardiac output can then result in inadequate renal perfusion and decreased eGFR.[50] Another possibility is that LA dysfunction promotes blood stasis and microembolism, which could potentially lead to renal infarcts. Furthermore, shared pathways, such as inflammation, oxidative stress, and endothelial dysfunction,[51,52]

FIGURE 2. Decision curves of CKD prediction models by participant's diabetes status. Example interpretation: Among participants without diabetes, at a 5-year risk threshold of 5%, the predicted net benefit was 2.95 per 100 participants in the model that added LA reservoir strain to the CKD risk prediction equation variables, meaning that there was a net 2.95 true-positive results per 100 participants. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; LA, left atrial. [a]In participants without diabetes, CKD risk variables included age, sex, race, eGFR, cardiovascular disease history, ever smoker, hypertension, body mass index, and albumin-to-creatinine ratio. [b]In participants with diabetes, CKD risk variables included age, sex, race, eGFR, cardiovascular disease history, ever smoker, hypertension, body mass index, albumin-to-creatinine ratio, diabetes medication use, insulin use, and HbA1c.

TABLE 3. Performance of Predictive Models for 5-Year Risk of CKD: The Atherosclerosis Risk in Communities Study[a]

	C-index (95% CI)	Change in C-index	χ^2 (*P*)	AIC
Participants without diabetes (n=2473)				
CKD risk prediction equation variables[b]	0.763 (0.725-0.800)	—	4.33 (.89)	1983.26
+LA reservoir strain	0.789 (0.753-0.825)	0.026 (0.005-0.051)	6.14 (.73)	1952.54
+LA conduit strain	0.774 (0.737-0.811)	0.011 (−0.003 to 0.028)	11.93 (.22)	1969.46
+LA contractile strain	0.781 (0.746-0.816)	0.018 (0.003-0.035)	6.67 (.67)	1966.20
Participants with diabetes (n=1,042)				
CKD risk predication equation variables[c]	0.701 (0.658-0.744)	—	4.19 (.90)	1791.43
+LA reservoir strain	0.732 (0.692-0.773)	0.031 (0.006-0.058)	11.13 (.27)	1770.29
+LA conduit strain	0.715 (0.673-0.757)	0.014 (−0.001 to 0.029)	6.56 (.68)	1784.95
+LA contractile strain	0.725 (0.685-0.766)	0.024 (0.002-0.047)	3.51 (.94)	1777.93

[a]Abbreviations: AIC, akaike information criterion; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; LA, left atrial.

[b]In participants without diabetes, variables included age, sex, race, eGFR, cardiovascular disease history, ever smoker, hypertension, body mass index, albumin-to-creatinine ratio.

[c]In participants with diabetes, variables included age, sex, race, eGFR, cardiovascular disease history, ever smoker, hypertension, body mass index, albumin-to-creatinine ratio, diabetes medication use, insulin use, HbA1c.

may also play a role in the relationship between LA function and CKD. Finally, although associations persisted after adjusting for covariates and in multiple sensitivity analyses, it is possible that shared risk factors may still explain our observations.

Strengths of this analysis include the relatively large sample size of Black and White older adults, the assessment of several LA function measures by 2D-echocardriograms, and the use of decision curve analysis to assess the clinical utility of LA function for CKD risk prediction. Some limitations should be noted. First, some incident CKD cases may have been missed, particularly among participants who did not attend follow-up study visits and had no measures of eGFR. However, by using a composite definition for CKD, we attempted to identify additional events using data from the US Renal Data System and hospital records.[21] Second, our study sample included older Black and White adults from 4 US communities. Therefore, our results may be less generalizable to other populations (eg, younger adults). However, given that the incidence of CKD is low in adults younger than 65 years,[53] our findings remain clinically relevant because the public health burden of CKD is greatest in older adults. Third, 5% of participants who had echocardiograms were missing LA function data. However, we used MICE to impute these data, and results were similar to the primary analysis. Fourth, given that our study population consisted of older adults (mean age, 75 years), it is possible that death precluded development of CKD. However, in a sensitivity analysis that accounted for the competing risk of death, LA function measures were still significantly associated with incident CKD. Finally, similar to other observational studies, residual confounding may exist.

CONCLUSION

Lower LA function is associated with a higher risk for CKD in community-based older adults. In addition, LA function measures improve CKD risk prediction and have a higher predicted clinical net benefit compared with the CKD risk prediction equation variables alone. Findings from this study suggest that LA function may be a novel risk factor for CKD and may be useful in identifying those at a high risk for CKD.

POTENTIAL COMPETING INTERESTS

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **ACE,** angiotensin-converting enzyme; **AF,** atrial fibrillation; **AIC,** Akaike information criterion; **ARIC,** Atherosclerosis Risk in Communities; **CKD,** chronic kidney disease; **eGFR,** estimated glomerular filtration rate; **HbA1c,** hemoglobin A1c; **LA,** left atrial; **LV,** left ventricular; **MICE,** multiple imputation by chain equation

Affiliations (Continued from the first page of this article.): Medical School, Minneapolis (J.L.R., A.O., L.Y.C.); Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis (A.A.E.); Institute of Cardiology, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy (R.M.I.); Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA (A.A.); Department of Medicine and Chronic Disease Research Group, Hennepin Healthcare (C.A.H.), University of Minnesota, Minneapolis; Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD (J.I., K.M., J.C.); Division of Cardiology, Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX (A.M.S.); and Cardiovascular Division, Brigham and Women's Hospital, Boston, MA (S.D.S.).

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Correspondence: Address to Wendy Wang, PhD, MPH, Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, 1300 S 2nd Street, Suite 300, Minneapolis, MN 55454 (wang5694@umn.edu).

ORCID

Wendy Wang: https://orcid.org/0000-0001-6025-0173

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