ARIC Manuscript Proposal #3529

PC Reviewed: 12/10/19 **Status: _____** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Echocardiographic parameters and subsequent risk of chronic kidney disease (CKD)

b. Abbreviated Title (Length 26 characters): Cardiac echo and CKD risk

2. Writing Group:

Writing group members: Junichi Ishigami, Manabu Hishida, Lena Mathews, Dalane Kitzman, Josef Coresh, Scott Solomon, Amil M. Shah, Kunihiro Matsushita, others welcome

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _JI__ **[please confirm with your initials electronically or in writing]**

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3. Timeline:

Data ascertainment for the present study has been already completed. Data analysis and manuscript preparation will be done in the next 6 months.

4. Rationale:

The cardiorenal syndrome indicates a bidirectional relationship between kidney dysfunction and cardiac dysfunction.[1-3] Given a number of previous studies, kidney dysfunction is established

as a risk factor of cardiovascular outcomes. However, studies exploring cardiac abnormality as a risk factor of kidney dysfunction is actually limited. Our recent report from the ARIC Study (MP#3139) has uniquely demonstrated diagnosed heart failure as a robust risk factor for end-stage renal disease (ESRD), with a stronger association for heart failure with preserved ejection fraction (HFpEF) relative to reduced ejection fraction (HFrEF). However, we cannot necessarily conclude the etiological contributions of systolic and diastolic cardiac dysfunction to kidney disease progression from that report, because several medications (e.g., diuretics) or procedures (e.g., coronary angiography) with kidney toxicity may be administered during heart failure diagnosis.

In this context, previous studies have reported several echocardiographic parameters predating kidney disease progression such as left ventricular mass, pulmonary artery pressure, and right ventricular systolic function.[4-12] However, there are a few caveats in these studies such as limited echocardiographic parameters,[5,6] selected clinical populations,[5,7-12] selected indications for echocardiographic assessment,[4,6,12] short (< 3 years) follow-up time,[6,8-10] and/or relatively small sample size.[6-11] To overcome these caveats, we propose to explore the prospective association between echocardiographic parameters and risk of adverse kidney outcomes (e.g., incident chronic kidney disease [CKD], incident end-stage renal disease [ESRD], CKD progression, estimated glomerular filtration rate [eGFR] decline) in participants of the Atherosclerosis Risk in Communities (ARIC) Study who attended visit 5 (2011-2013) and underwent echocardiography tests.

5. Main Hypothesis/Study Questions:

Echocardiographic parameters are associated with the risk of adverse kidney outcomes (e.g., incident CKD, incident ESRD, CKD progression, eGFR decline)

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Design and analysis plan

- Study population: Our primary analysis will include all ARIC participants who attended visit 5 and underwent echocardiography tests. We will exclude if they reported race other than black or white, had eGFR < 15/ml/min/1.73m^2. We will repeat the analysis with limited number of echocardiographic parameters evaluated at visit 3 among Jackson site participants.

Exposures:

The primary exposures will be echocardiographic parameters measured at visit 5 (and 3) (**Table**). Parameters will be indexed to body surface area as appropriate.

Table: Echocardiographic parameters

LV vs. RV	Category	Parameter	V5 variable	V3	Measure
LV related	LV mass	Left ventricular mass (LVM)	ech11, 12	Yes	A marker for CVD and premature death

		Relative wall thickness (RWT)	ech13	No	Measure of LV geometry. Can be used in combination with LVMI
	LV size	LV end-diastolic volume (LVEDV)	ech8	No	
		LV end-systolic volume (LVESV)	ech9	No	
		LV end-diastolic diameter (LVEDD)	ech4	Yes	
		LV end-systolic diameter (LVESD)	ech5	Yes	
	LV systolic function	Ejection fraction (EF)	ech10	Yes	Ejection fraction
		Left ventricular outflow tract velocity time integral	ech31	No	Measure of cardiac systolic function and cardiac output
		Mid-wall fractional, longitudinal, and circumferential strain	ech47	No	Average peak longitudinal strain (%)
		Tissue Doppler mitral annular peak systolic velocity (TDI S')	ech5, 6	No	left ventricular systolic function
		EA/EES	ech45 (ech43/ ech44)	No	LV- arterial elastance (EA)/ end-systolic elastance (EES), reflecting global cardiovascular efficiency
	LV diastolic function	Left atrial volume (LAV)	ech16, 17	Yes	Chronic marker for LV filling pressure
		E wave	ech20	Yes	Early ventricular filling velocities
		A wave	ech21	Yes	Late ventricular filling velocities
		E-A ratio	ech28	Yes	Diastolic performance
		E wave deceleration time	ech22	No	E wave deceleration time (mm per sec)
		Isovolumetric relaxation time	ech23	No	Indicator for diastolic function
		E wave/ E' ratio	ech29, ech20/ech26	No	Instantaneous LV filling pressure
		Tissue Doppler imaging E' (TDI E')	ech24, ech26	No	Early diastolic relaxation
RV related	RV systolic function	RV fractional area change	ech38	No	Measure for RV ejection fraction ([(RVEDA-RVESA)/RVEDA]×100%.)
		RV end diastolic area	ech36	No	Apical 4 chamber view: RV end diastolic area (cm^2)
		RV end systolic area	ech37	No	Apical 4 chamber view: RV end diastolic area (cm^2)
		RV volume	ech36-38	No	Calculated using Simpson's method
		Tricuspid annular peak systolic myocardial velocity	ech39	No	TDI tricuspid annular S' cm per sec? Measure for RV function
	Pulmonary hemodynamics	Peak tricuspid regurgitation velocity	ech40	No	Marker for PASP
		Peak RV-RA gradient	ech41	No	mmHg

		Pulmonary Vascular Resistance	ech42	No	Wood Units (calculated as TRV/TVIRVOT?)

Outcomes:

The primary outcome of interest is kidney disease progression as defined by the composite outcome of incident ESRD or incident CKD (among those w/o CKD at baseline) or worsening kidney function (≥ 30% eGFR decline at visit 6 or 7). We will explore other kidney outcomes as the secondary outcomes (**Table**).

Table: Kidney outcomes

Outcomes	Variable	Definition	Analytic approach
Primary outcome			
Composite outcome	Binary	Incident ESRD or incident CKD (among those w/o CKD at baseline), or worsening kidney function (≥ 30% eGFR decline at visit 6 or 7)	Time-to-event
Secondary outcomes			
Incident ESRD	Binary	ESRD with linkage to USRDS or death due to CKD	Time-to-event
Incident CKD	Binary	Incident ESRD or hospitalization with CKD or eGFR < 60 ml/min/1.73m^2	Time-to-event
Incident albuminuria	Binary	ACR ≥ 30 mg at visit 6 or 7	Time-to-event
Scr doubling (57% eGFR decline)	Binary	Scr doubling between visit 5 and visit 6 and 7	Time-to-event Logistic regression
eGFR decline (30%, 40%)	Binary	eGFR decline between visit 5 and visit 6 and 7	Time-to-event Logistic regression
Composite outcome	Binary	Incident ESRD or incident CKD (among those w/o CKD at baseline) or worsening kidney function (≥ 30% eGFR decline) or UACR progression	Time-to-event
eGFR slope	Continuous Categorical	eGFR slope between visit 5 and 7	Mixed effect model
eGFR change, absolute	Continuous Categorical	Absolute change in eGFR between visit 5 and visit 6 or visit 7	Mixed effect model
eGFR change, relative	Continuous Categorical	% change in eGFR between visit 5 and visit 6 or visit 7	Mixed effect model

Other variables of interest:

-Age
-Race
-Sex
-Body mass index (BMI)
-Blood pressure (systolic and diastolic)
-Smoking status
-Alcohol consumption
-Education level from visit 1
-CKD measures (eGFR, urinary albumin to creatinine ratio [ACR])
-Lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol, triglyceride)
-Inflammatory markers (high sensitivity C-reactive protein [hs-CRP])
-Medication use:
    -Aspirin

-Statin
-Antihypertensive medication (e.g., ACEi, ARB, β-blocker)
-Diuretics
-Medical history:
-Diabetes mellitus (DM)
-Hypertension
-Cancer
-Liver disease
-Chronic obstructive pulmonary disease (COPD)
-Prior CVD (heart failure, coronary heart disease, stroke, atrial fibrillation, peripheral artery disease)

Statistical analysis plan:
-Baseline characteristics will be compared across categories of echocardiographic parameters using chi-square tests and analysis of variance.
-Estimate incidence rates and 95% confidence intervals with Poisson regression models
-Estimate hazard ratios and 95% confidence intervals with Cox proportional hazard models
-Models will be adjusted for age, sex, race-center, BMI, smoking status, alcohol consumption, educational level, aspirin use, antiplatelet use, history of hypertension, diabetes, eGFR, ACR, total cholesterol, HDL cholesterol.
-eGFR slopes will be assessed using mixed effects models with unstructured residual correlation matrix to account for within-subject correlation with a random intercept.
-Sensitivity analysis adjusting for incident CVD as a time-varying covariate.
-Subgroup analyses by sex (men vs. women), age (<65 vs ≥65 years), race (black vs. white), DM (yes vs. no), hypertension (yes vs. no), prevalent CVD (yes vs. no), eGFR (<60 vs ≥60 ml/min/1.73m^2), ACR (<30 vs ≥30 mg/g).

Limitations:
-Residual confounding
-Reverse causation
-Study population restricted to older adults residing in the community

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes _X__ No

b. If Yes, is the author aware that the file ICTDER03 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? ____ Yes ____ No
(This file ICTDER has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ____ Yes _X_ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ____ Yes ____ No

9. **The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.** ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html

__X__ Yes _____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

MP#1972 The association of kidney disease measures with left ventricular and atrial structure and function: The Atherosclerosis Risk in Communities (ARIC) Study

- This manuscript proposal explored the cross sectional association between kidney disease measures and left ventricular and atrial structure and function. Our proposal will explore the prospective association between cardiac structure and the subsequent kidney outcomes. The lead author of MP#1972, Dr. Kunihiro Matsushita, is included in the writing group for the present proposal. We also welcome other investigators to join the writing group.

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X_ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number at https://www2.cscc.unc.edu/aric/approved-ancillary-studies

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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