1.a. **Full Title**: Diastolic wall strain and incident cardiovascular events in African Americans: Results from the Atherosclerosis Risk In Communities (ARIC) Study

b. **Abbreviated Title (Length 26 characters)**: DWS and CV events

2. **Writing Group**: Writing group members: Daisuke Kamimura, MD, PhD; Takeki Suzuki, MD, MPH, PhD; Michael E. Hall, MD; Kenneth R Butler, PhD; Ervin Fox, MD, MPH; Thomas H. Mosley, PhD; others welcome

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

**First author**: Daisuke Kamimura, MD, PhD  
Address: Division of Cardiology / Department of Medicine  
University of Mississippi Medical Center  
2500 North State St. Jackson, MS 39216  
Phone: 601-984-4607  
Fax: 601-984-5608  
E-mail: dkamimura@umc.edu

**ARIC author** to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).

**Name**: Thomas H. Mosley, Jr., PhD  
**Address**: Department of Medicine-Geriatrics  
2500 N State Jackson, MS 39216  
Phone: 601.984.2763  
Fax: 601.815.3422  
E-mail: tmosley@umc.edu

3. **Timeline**: Data to be used in this proposal are currently available. Analyses and manuscript preparation will be performed over the next 6 months

4. **Rationale**: Aortic and left ventricular (LV) stiffness are risk factors for cardiovascular morbidity and mortality (1,2). Aortic stiffness has been reported to be associated with incident stroke (3),
coronary heart disease (4), and cardiovascular and all-cause mortality (5). LV stiffness is closely related to aortic stiffness through ventricular arterial coupling (6). As LV stiffness is measured invasively, there are no practical and noninvasive methods with which to evaluate aortic and LV stiffness non-invasively. Diastolic wall strain (DWS) is a recently developed indicator to evaluate the LV stiffness directly and non-invasively by echocardiography (7). DWS is calculated from LV posterior wall at systole and diastole as (LV posterior wall thickness at end-diastole - LV posterior wall thickness at end-systole) / LV posterior wall thickness at end-systole. DWS has been shown to be correlated with the LV stiffness indicator in animal models and in patients with heart failure with preserved ejection fraction (HFpEF) (7). A lower value of DWS is suggestive of increased LV myocardial stiffness, which was associated with a poor prognosis in HFpEF patients, and a risk factor for HFpEF in diabetic patients (2,8). Furthermore, a lower DWS has been associated with adverse LV remodeling even in patients with normal left ventricular diastolic function (9). Lastly, DWS has been shown to be associated with myocardial fibrosis markers such as carboxy-terminal propeptide of procollagen type I (10). On the other hand, no previous studies looked at association between LV stiffness and clinical factors.

We hypothesized that LV structure remodeling and deterioration of cardiac function, evaluated by DWS, is associated with high cardiovascular (CV) events, CV mortality, and all-cause mortality in the Jackson cohort of the ARIC study. We also hypothesized that DWS is associated with incidence HF. Lastly, we propose to evaluate the relationship between DWS and clinical factors.

5. Main Hypothesis/Study Questions:

**Hypothesis 1:** DWS, calculated as (LV posterior wall thickness at end-diastole - LV posterior wall thickness at end-systole) / LV posterior wall thickness at end-systole, is associated with increased risk of CV events.

**Hypothesis 2:** DWS is associated with incident HF, CV mortality, and all-cause mortality.

**Hypothesis 3:** DWS is associated with patients’ sociodemographic parameters, dietary intake, medical history, medications, physical activity, and other cardiac function indicators.

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).

**Inclusions:** All the ARIC subjects who underwent echocardiography at exam 3 (1993-1995). The echocardiography was performed at the Jackson field center.

**Exclusions:**

Subjects with HF, significant valvular diseases, LVEF < 50%, segmental LV wall motion abnormality

Subjects with atrial fibrillation or flutter at baseline (AF/AFL)

Subjects without echocardiography measurements
Subjects with missing baseline clinical characteristics

**Data at Exam 3** will be used.

**Sociodemographics (Exam 3):**

- age (V3AGE31), gender (GENDER), race (RACEGRP), Education

**Physical information (Exam 3):**

- height (ANTC1), weight (ANTC2), BMI (BMI32), BSA (Calculate from ANTC1 and 2),
- Waist Hip circumferences (ANTC3A, ANTC3B, WSTHPR31), systolic blood pressure (SBPC22 or ECHA7), diastolic blood pressure (SBPC23, ECHA8), heart rate (ECGMC31, or ECHA62)

**Lifestyle (Exam 3):**

- Smoking status (Ever SmokerEVRSMK31, Current Smoker CURSMK31)
- Alcohol consumption (Current CURDRK31, Ever EVRDRK31)
- Dietary intake (DTIC 2-93), Nutrition (NUTV3, Vitamin and Nutrient Data)
- Physical activity (RPAC1,2)

**Comorbidities (Exam 3):**

- History of hypertension (HYPERT35), diabetes (Diabts34)
- Heart failure (PHXA8J) Coronary heart disease (PRVCHD32), Stroke

**Chemistry (Exam 3):**

- Hemoglobin (HMTC4), Hematoctit (HMTC5)
- Cholesterol (LIPC1A), Triglyceride (LIPC2A), HDL (LIPC3A), LDL (LIPC5)
- Glucose (LIPC4A)

**Medication use (Exam 3):**

- High blood pressure (MSRC24A), High blood cholesterol (MSRC24B), Angina or chest pain (MSRC24C), Heart Failure (MSRC24E), Diabetes or High blood sugar (MSRC24G)

**Echocardiography parameters (Exam 3):**
LVDd (ECHA41(m-mode),51(2D)), LVDs (ECHA42(m-mode), 52(2D)), LV end-diastolic volume (LVEDV):
7*LVDd^3/(100*(LVDd+2.4)), LVEnd-systolic volume (LVESV):
7*LVDs^3/(LVDs+2.4)), SV: LVEDV - LVESV ,
LV regional wall motion (ECHA14)
LV posterior wall thickness at end-systole/end-diastole (ECHA44(m-mode),55(2D))
/ECHA43(m-mode),54(2D)
LV septum wall thickness at end-systole/end-diastole (ECHA40(m-mode),50(2D))
/ECHA39(m-mode),49(2D)
LVMI (ECHA58/BSA), Relative wall thickness (RWT): (2*LWPWd/LVDd),
LV ejection fraction (EF): 100*SV/LVEDV, LV fractional shortening (FS) (ECHA47(m-mode), 53(2D)).
E wave velocity (ECHA 68), A wave velocity (ECHA 69)
Ratio of MV peak E to Peak A (E/A) (ECHA70)

Aortic root diameter (ECHA46(m-mode), 57(2D)), Left atrium diameter (ECHA45(m-mode), 56(2D)).
Indicator of LV myocardial stiffness: Diastolic wall strain (PWs - PWd) / PWs

**Outcomes:**

*(Hypothesis1)*

CVD events, defined as stroke, HF, MI, fatal CHD

Stroke: (Event: C7_IN12DP, C7_IN12ISC, C7_IN12CHM, Date: C7_ED12DP, C7_ED12ISC, C7_ED12CHM)

HF: (Event: C7_INCHF12, Date: C7_DATE_INCHF12)

MI or fatal CHD: (Event:C7_IN_12S, Date:C7_DATEIS)
Brief Statistical Analysis Plan:

**Hypothesis 1:** DWS is associated with risk of CV events

We will use DWS measured by echocardiography at baseline.

Kaplan-Meier curve will be constructed based on two groups categorized by median value of DWS.

The associations between DWS and events will be evaluated using Cox proportional hazards models. DWS will be used as continuous variables in the models. We will adjust for covariates listed above. Model 1 will include baseline demographics (age, gender, and education) and model 2 the following factors: model 1 plus CHD, body mass index, and conventional coronary risk factors (sBP, dBP, use of HTN meds, TC/HDL ratio, LDL cholesterol, diabetes mellitus, current smoking). Model 3 will include model 2 plus incident CHD and HF as time-varying variables.

Stratified analysis will be performed based on age, gender, HTN, DM, obesity, baseline CHD.

**Hypothesis 2:** DWS is associated with CV mortality, all-cause mortality, and incident HF.

The same analyses of time to event from baseline will be performed for HF.

**Hypothesis 3:** DWS is associated with patients’ sociodemographic parameters, blood pressure, physical information, lifestyle, comorbidities, chemistry, medication use, echocardiographic parameters in African Americans.

In order to evaluate clinical determinants of DWS comprehensively, we will perform cross-sectional analyses using the data from exam3. The correlation between DWS and several parameters will be examined by linear regression. Independent predictors for DWS will be obtained with use of stepwise multiple linear regression analysis. In multiple linear regression, variables with a univariate value of $P < 0.05$ were used for the forward stepwise multiple regression models.

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.csc.unc.edu/ARIC/search.php

_ 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)?

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 http://www.csc.unc.edu/aric/forms/

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.csc.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.
13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript _____ Yes __X__ No.

References
8. Ohtani T, Mohammed SF, Yamamoto K et al. Diastolic stiffness as assessed by diastolic wall strain is associated with adverse remodelling and poor outcomes in heart failure with preserved ejection fraction. Eur Heart J 2012;33:1742-9.