ARIC Manuscript Proposal #3866

PC Reviewed: 6/8/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1. a. Full Title:
Diabetes and left atrial function: The Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title:
Diabetes and LA function

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

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3. Timeline:
June 2021-August 2021 – Complete primary data analysis
October 2021-January 2022 – Additional data analysis/Manuscript preparation
February 2022—Submit abstract ASE scientific sessions
June 2022-July 2022 – Submit manuscript for P&P review

4. Rationale:
During the initial stages of left ventricular diastolic dysfunction (LVDD), changes in left atrial (LA) structure and function help to preserve cardiac output. However, over

time, these changes can become maladaptive and LA dysfunction ensues, resulting in a reduction in LA compliance, rise in LA pressure, and consequent LA failure.[1] The progression to LA dysfunction is thought to play an important role in the transition from left ventricular diastolic dysfunction (LVDD) to heart failure with preserved ejection fraction (HFpEF).[2-5] Amongst individuals with diabetes, LA dysfunction has been associated with an increased risk of composite cardiovascular events, which include heart failure (HF), atrial fibrillation (AF), coronary heart disease (CHD), and stroke.[6, 7]

LA function has 3 phases, serving as a reservoir in systole, as a conduit in early diastole, and as a booster pump in late diastole.[8] The prevalence of LVDD in individuals with diabetes is significantly higher than in the general population, and these individuals are considered to be particularly prone to LA dysfunction.[9, 10] This is due to a variety of mechanisms that promote LA remodeling. These mechanisms include decreased LA wall elasticity, increased oxidative stress and inflammation, increased renin-angiotensin-aldosterone activity, increased sympathetic activity, LA conduction disease, increased blood pressure associated with insulin resistance, and LA subendocardial fibrosis.[11]

Current data examining the association of diabetes with LA function, measured via either emptying fraction calculation or strain technique, suggest that (1) LA function is worse in those with diabetes compared to those without, and that (2) LA function is worse in those with poorly-controlled diabetes compared to those with controlled diabetes.[12-17] These studies, however, were limited by small sample sizes. Thus, we will evaluate the associations of diabetes status, diabetes severity, and diabetes duration with left atrial function in a well-characterized, large population-based cohort. LA function measures will include volumetric and strain-based indices at ARIC visit 5.

5. Study Objective:

Aim 1: Evaluate the association of diabetes status at Visit 5 (V5) with LA function at V5

Aim 2a: In participants with diabetes, evaluate the association of diabetes control (as defined by HbA1c) with LA function at V5
Aim 2b: In participants with diabetes, evaluate the association of diabetes duration with LA function at V5

Aim 3: In participants without diagnosed diabetes, examine the association of blood glucose (fasting glucose and HbA1c) with LA function at V5

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).

Data:

Study participants

Members of the ARIC cohort attending Visit 5 (2011-2013) with data for echocardiographic measures of left atrial function (n=5784).

Exposure variables—Diabetes

1) *Fasting serum glucose level (V5)*

2) *Hemoglobin A1c level (V5)*
3) *Diabetes status at (V5)* —no diabetes vs. diabetes
   - Diabetes will be defined as self-reported physician diagnosis of diabetes or use of glucose-lowering medication
4) *Diabetes duration*
   - Information from visits 1–4 and annual follow-up calls following visit 4 will be used to identify the date of first reported diabetes. Diabetes duration will be calculated as the difference between this date and the visit 5 date. Self-reported diabetes in ARIC has been shown to be reliable and highly specific.[18] Participants who reported no diabetes at any visit or phone call prior to visit 5 but who meet the definition of diabetes at visit 5 will be categorized as having diabetes with 0 duration.

Outcome variable— Left atrial function

From LA strain analysis, LA phasic function was estimated using: peak strain during systole to assess reservoir function, early peak strain during diastole to assess conduit function, and late peak strain during diastole to assess contractile function.

- *Left atrial reservoir function*
  LA total emptying fraction (LA total EmF) = (LA maximal volume (LAV_{max}) – LA minimal volume (LAV_{min}))/LAV_{max} x 100
- *Left atrial conduit function*
  LA passive EmF = (LAV_{max} – LA volume before onset of the P wave on the ECG tracing (LAV_{preA}))/LAV_{max} x 100
- *Left atrial contractile function*
  LA active EmF = (LAV_{preA} – LAV_{min})/LAV_{preA} x 100

Covariates

Demographic – Age (y), Sex, Race by Clinic site (5-category variable), Educational attainment

Physical examination – SBP (mmHg), DBP (mmHg), Height (cm), Weight (kg), BMI (kg/m^2)

Comorbidities – Cigarette smoking (current/former/never & pk-yr), Hypertension (yes/no), Heart failure (yes/no), Coronary heart disease (yes/no), Atrial fibrillation/flutter (yes/no)

Echocardiographic data – Left atrial volume index (LAVI), E/e', Left ventricular mass index (LVMI)

Laboratory data – eGFR by CKD-EPI cystatin ($mL/min/1.73m^2$), hs-CRP (mg/L)

Medication use (yes/no) –Anti-hypertensive use

**Hypertension will be based off SBP, DBP, and Anti-hypertensive use

Exclusion criteria

Individuals without V5 diabetes, covariate, or LA function data will be excluded.

Analysis plan:

Eligible participants not meeting any of the exclusion criteria above will be part of the study analysis.

1) Comparison of baseline characteristics

   Descriptive statistics will be computed for baseline characteristics. We will examine the distributions of exposure variables stratified according (1) diabetes status

(diabetes vs. no diabetes), (2) diabetes control (HgbA1c <7 vs. >7), and (3) diabetes duration (<10 years vs. ≥ 10 years).

2) Association of diabetes status with left atrial function

Multivariable linear regression will be used to assess the association of LA function parameters with diabetes status. Associations will be adjusted as follows:

Model 1: Age, Sex, Race by Clinic site, and Educational attainment

Model 2: Model 1 + SBP, BMI, Cigarette smoking, HF, CHD, AF, eGFR, hs-CRP, and anti-hypertensive use

Model 3: Model 2 + LAVI, LVMI, and E/e'

3) Association of blood glucose with left atrial function in individuals without diabetes

Multivariable linear regression will be used to assess the associations of LA function with fasting glucose. Associations will be adjusted for covariates listed above.

4) Association of diabetes control with left atrial function in individuals with diabetes

Multivariable linear regression will be used to determine (1) differences in LA function according to glucose control (HgbA1c <7 vs. ≥7 and quartiles) and (2) regression (β) coefficients per 1 SD increment of HgbA1c for each of the LA function parameters. Associations will be adjusted according to models above.

5) Association of diabetes duration with left atrial function in individuals with diabetes

Multivariable linear regression will be used to determine (1) differences in LA function according to diabetes duration (<10 years vs. ≥10 years) and (2) regression (β) coefficients per 1 SD increment of duration (years) for each of the LA function parameters. Associations will be adjusted according to models above.

6) Sensitivity analysis excluding individuals with HF or AF at V5

We will repeat step 2 excluding individuals with either HF or AF at V5 as both conditions may distort associations between diabetes and LA function

7. a. Will the data be used for non-CVD analysis in this manuscript?

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?

8. Will the DNA data be used in this manuscript?

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.

YES

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)?

The author identifies no significantly related manuscript proposals. Co-authors with extensive ARIC experience for prior proposals related to echocardiographic measures and diabetes have been contacted to collaborate.

11. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?

YES—" Chen, 2015.29 (PI: Lin Y Chen)

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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