ARIC Manuscript Proposal #3761

PC Reviewed: 1/12/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Duration of Diabetes and Incident Heart Failure: the Atherosclerosis Risk in Communities (ARIC) Study

b. Abbreviated Title (Length 26 characters): **Diabetes duration & Heart Failure**

2. Writing Group:

Writing group members: Justin Echouffo-Tcheugui, Sui Zhang, Roberta Florido, James Pankow, Erin Michos, Ronald Goldberg, Roger Blumenthal, Vijay Nambi, Christie Ballantyne, Joe Coresh, Liz Selvin, Chiadi Ndumele; others welcome

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

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3. Timeline: We aim to complete the manuscript within 1 year from the time of approval.

4. Rationale:

Diabetes and heart failure (HF) are highly prevalent[1,2] and strongly interrelated.[3,4] Community-based studies have shown that diabetes is a potent risk factor for HF, raising the risk by 2 to 5-fold.[3,4] However, the extant studies have either not or seldom examined the effect of diabetes duration on the incidence of HF,[5,6] and have not always accounted for the degree or extent of glycemic control Indeed, an autopsy study demonstrated an association between

diabetes duration and the extent of intrinsic myocardial lesions, not always related to coronary artery disease. [7] This data combined with our knowledge of the possible effects related to the unquantified period of hyperglycemia prior to diagnosis,[8] suggests that the duration of diabetes will significantly affect HF incidence. Knowledge of the independent effect of diabetes duration on the incidence of HF can help guide a more effective identification of high-risk diabetic patients, who may benefit from more aggressive initiation of cardioprotective preventative therapies, especially in the context of emerging novel therapies such as sodium-glucose co-transporter-2 (SGLT2) inhibitors. [9,10]

Studies of diabetes and incident HF have been limited in their ability to identify the onset of diabetes due to lack of antecedent measures of glycemia.[3,4,7] In the ARIC study, from Visit 1 to Visit 4, blood glucose and clinical diagnoses of diabetes were assessed every 3 years, enabling a relatively accurate assessment of the inception of diabetes. Although diabetes is also strongly associated with the development of atherosclerotic cardiovascular disease, the multitude of data suggesting independent effects of diabetes on the myocardium suggests that any association between diabetes duration and incident HF will persist even after adjustment for intervening ischemic events.[11]

Using Visits 1 to 4 data from the ARIC study, we aim to assess the effect of diabetes duration on incident HF among Visit 4 participants, hypothesizing that a longer duration of diabetes is associated with a greater likelihood of the development of HF, independent of age, other comorbidities, intervening coronary heart disease events, and of the degree of blood glucose control (as assessed by glycosylated hemoglobin [A1C]). We will further examine whether there are demographic differences in the association between diabetes duration and HF, testing for interactions by age, sex and race.

5. Main Hypothesis/Study Questions:

Aim 1: Examine whether longer diabetes duration is independently associated with incident HF, as compared to those without diabetes.

Aim 2: Examine whether the association between diabetes duration and HF, differs by the extent of glycemic control and the age of participants. Such an examination will allow the separation of the intrinsic effect of diabetes duration from that of glucose control and age.

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:

Prospective cohort study of Visit 4 participants, examining the association of diabetes duration (based on self-reported data on diabetes status and glycemic assessments, from Visit 1 through Visit 4, as well as data on self-reported age of diabetes diagnosis collected at Visit 3) with incident HF events occurring after visit 4. We will include individuals with and without diabetes, with the latter serving as the reference group in analyses.

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Exclusions:

We will exclude individuals with missing data on diabetes status at each of the first 4 visits, and on key covariates at Visit 4. We will exclude individuals with HF diagnosis before or at Visit 4.

We will also exclude those of non-Black or non-White race due to small numbers, and Blacks at Washington County and in Minnesota.

Exposures:
Diabetes duration will be the primary exposure.

Diabetes status will be defined as a prior physician diagnosis of diabetes, use of hypoglycemic medications, a fasting blood glucose ≥126 mg/dL or a non-fasting blood glucose ≥ 200 mg/dL.

Diabetes duration will be assessed using data from Visit 1 to Visit 4, in two ways:

- We will examine diabetes diagnosis history by using a categorical variable that indicates the ARIC study visit of diabetes diagnosis (diagnosis at Visit 4 [1996–1999], diagnosis at Visit 3 [1993-1995], diagnosis at Visit 2 [1990–1992] , diagnosis at Visit 1[1987–1989]), with those without diabetes at visit 4 being the comparator. We will also create an additional category for those with prediabetes at Visit 4. Once diabetes is diagnosed, it will be assumed to be present thereafter.
- We will calculate the duration of diabetes using the data on diabetes status from each visit (Visit 1 to Visit 4) as well as data on the self reported age of diabetes diagnosis (collected at visit 3). We will specifically use self-reported age of diabetes diagnosis to calculate the duration of diabetes for those with a prior physician diagnosis or use of hypoglycemic medications at Visit 1. We will model the duration of diabetes in two ways. We will first categorize duration as: 1-5 years, 5 to 10 years, 10 to 15 years, and more than 15 years (the latter 2 groups may be collapsed in stratified analyses as needed for adequate power). We will also model duration continuously and estimate HF risk per year of diabetes duration.

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Covariates
Visit 4 measures of age, sex, race-center, smoking status, body mass index, total cholesterol, HDL-cholesterol, systolic blood pressure, hypertension medication use, estimated glomerular filtration rate (eGFR), and prevalent coronary heart disease. We will also incorporate hemoglobin A1C (A1C) from Visits 2 and 4, in analyses considering glycemic control as an effect modifier of the association between diabetes duration and HF. As A1C was not measured at visit 4, we will use measures of glycated albumin to derive A1C, especially as correlation between glycated albumin and A1C is high (~0.86). through a regression model developed using measured A1C and glycated albumin at Visit 2. We will also consider imputing A1C values at visit 1 and 3.
In additional analyses, we will consider adjustment for incident CHD after visit 4 as a time-varying covariate.
We will also consider adjustment for covariates at both visit 1 and visit 4, to partially account for their changes over time.

Outcomes:
Our main outcome is incident HF hospitalization or death after visit 4, defined by ICD codes.

Statistical Analysis:

We will derive descriptive statistics for the characteristics of participant at baseline (Visit 4) according to the timing of diabetes onset (Visit 1, Visit 2, Visit 3, Visit 4 or absent by Visit 4). The chi-square test will used for comparison of categorical variables and the appropriate parametric or non-parametric test for continuous variables.

Cox proportional hazards survival models will be developed to examine the association between the diabetes duration (principally modeled categorically as described above) and the development of HF, as compared to individual without diabetes. We will also assess risks of HF per year of diabetes duration. In all analyses, we will assess duration of diabetes and incident HF using sequential modelling as follows:

- Model 1 : adjusted for age, sex and race/center
- Model 2: Model 1 + smoking status, body mass index, systolic blood pressure, use of blood pressure medications, total-cholesterol/HDL-cholesterol ratio, eGFR, and coronary heart disease
- In sensitivity analyses, we will adjust for incident CHD after Visit 4 as a time-varying covariate,
- In additional sensitivity analyses we will consider adjusting for covariates at both visit 1 and visit 4, to account for changes over time.

To more flexibly assess the association between duration of diabetes and incident HF by allowing for deviations from linearity, we will conduct restricted cubic spline modelling.

We will conduct a priori stratified analyses, with stratification by the degree of blood glucose control (categorized as ≥7% at either Visit 2 or 4 or < 7% at both visits), and by age (categorized as ≥65 or < 65 years) to try and separate out the intrinsic effect of the duration of diabetes from that of the degree of blood glucose control and of the age of participants. We will also conduct a priori stratified analyses by race and sex. We will test for interactions of diabetes duration with glycemic control, age, sex and race.

Secondary Analysis:
In a secondary analysis, we will consider creating separate categories for diabetes at Visit 1 diagnosed by glucose at the study visit only, versus diabetes diagnosed previously by a physician or the use of hypoglycemic medications.

Limitations:

- Residual confounding due to the observational nature of the study.
- Lack of clarity regarding the exact timing of diabetes onset between 3-year visits from visits 1 to 4.
- Survival bias associated with performing analysis among Visit 4 participants without HF, who are generally healthier than those with HF events or death prior to Visit 4. However, this is likely a conservative bias for assessing the association of diabetes duration with incident HF.

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/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)?
MS Proposal # 1125 - Diabetes, obesity and insulin resistance as risk factors for incident hospitalized heart failure: The Atherosclerosis Risk in Communities (ARIC) Study
MS Proposal #3536 - Association of Glycemic Status and Heart Failure subtypes (preserved ejection fraction vs. reduced ejection fraction) among Older Adults: The Atherosclerosis Risk in Communities Study.
MS Proposal #3537 - Association of Glycemic Status and Progression of Cardiac Dysfunction among Older Adults: The Atherosclerosis Risk in Communities Study
No prior proposal on the duration of diabetes and incident HF.

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

11.b. If yes, is the proposal
_x__ A. primarily the result of an ancillary study (list number* _ AS2017.27___)
___ 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.cscc.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.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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