ARIC Manuscript Proposal #3401

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Full Title: Risk Determinants and Prediction of Heart Failure Among Patients with Prediabetes or Type 2 Diabetes Mellitus: A Pooled Multi-Cohort Analysis

b. Abbreviated Title (Length 26 characters): HF risk prediction in patients with diabetes

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3. Timeline: Manuscript Submission: June 2020  
Abstract presentation target for AHA Scientific sessions 2020

4. Rationale: Prevention of atherosclerotic cardiovascular disease (ASCVD) events has been a major goal of therapeutic approaches in type 2 diabetes mellitus (T2DM) in the assessment of therapies in randomized cardiovascular outcomes clinical trials and in clinical practice guidelines and consensus recommendations.(1)  
Similarly, since the 2008 US Food and Drug Administration guidance to industry requiring cardiovascular (CV) outcomes assessment for all new therapies for T2DM, the statistical exclusion of significant incremental risk with regard to a composite of major adverse CV events (MACE) has been the focus of CV outcomes trial programs of novel and established antihyperglycemic therapies over the last decade.(2) There is comparatively less attention towards formal evaluation of the effects of antihyperglycemic therapies on incident and worsening heart failure (HF), despite its frequency as an initial presentation of CV disease and high prevalence in T2DM.(3) Patients with T2DM with adequate control of major CV risk factors within target ranges appear to have comparable risk of ASCVD to the general population; however, even patients with T2DM with no additional CV risk factors face a substantial residual risk of hospitalization for HF.(4,5) Unfortunately, these patients with T2DM complicated by HF experience a particularly high burden of HF-related morbidity and high mortality risk.(6) As such, the prevention of HF in T2DM is of utmost importance.  
The sodium-glucose cotransporter 2 (SGLT2) inhibitors, a class of antihyperglycemic therapy, have been shown to reduce risk of HF hospitalization-incident and recurrent-in patients with T2DM at high CV risk,(7-9) and are now recommended as a second-line therapy (after metformin) in patients with T2DM and prevalent ASCVD or at high ASCVD risk.(10,11) However, limited guidance is available regarding targeted introduction of SGLT2i’s in patients with T2DM at heightened risk of HF with and without established ASCVD. Accordingly, in this study proposal, we plan to identify the clinical predictors of development of HF among patients with pre-diabetes or T2DM without prevalent HF and develop a simple, integer-based clinical score that can identify patients at sufficient risk for incident HF to justify primary prevention use of SGLT2i’s. Because of the proven efficacy of SGLT2 inhibitors in preventing and treating HF in patients with T2DM, such a score could help identify patients who would benefit from these novel therapies. Thus, such a score would have the potential for immediate clinical impact.
5. **Main Hypothesis/Study Questions**: To identify the correlates of incident HF among patients with prevalent pre-diabetes or T2DM without prevalent HF and develop a parsimonious clinical risk score to identify such patients at increased risk for HF who may benefit from primary HF prevention therapies.

**Hypothesis**: We hypothesize that clinical risk factors and serum biomarkers, like high sensitivity troponin, natriuretic peptides, and high-sensitivity C-reactive protein can be used to develop a sufficiently discriminating risk prediction model for incident HF among patients with pre-diabetes or T2DM to inform clinical decision making.

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)**.

**Sample inclusion criteria**:
- Participants of ARIC, DHS, CHS, and MESA with available glycated hemoglobin (HbA1c) or fasting plasma glucose and prevalent diagnosis of T2DM and HF at baseline

**Exclusion criteria**:
- Participants with missing baseline information on CVD status, HF status, DM status, HbA1c level, fasting plasma glucose
- Participants with prevalent HF at baseline

**Primary outcome of interest**: Incident HF event: The definition and adjudication procedure for HF events have been previously reported for each of three study cohorts.(12-14) In ARIC, continuous, retrospective surveillance of hospital discharges for HF were conducted for all residents from the four US communities included in the study. A hospitalization was considered eligible for confirmation as a HF event based on its International Classification of Disease, 9th Revision, and Clinical Modification (ICD-9-CM) code.(13,15) In the DHS, incident HF was determined through a detailed annual health survey regarding interval CV events, and/or via quarterly tracking for hospital admissions using the Dallas-Fort Worth Hospital Council Data Initiative database.(14) In MESA, participants were contacted every 9-12 months, and information regarding new CV conditions, hospitalizations and treatments was obtained. Further classification of CV events also occurred from collection of death certificates, medical records from hospitalizations, autopsy reports, and interviews with or questionnaires administered to participants, relatives, or physicians.(12) For the proposed pooled analyses, we would include all HF events from the baseline visit through 10 years of follow up for each individual study cohort.

**Covariates of Interest**:
- Age, sex, ethnicity, body mass index, waist circumference, physical activity levels, baseline HbA1c, baseline clinic systolic and diastolic blood pressure, history of T2DM, hypertension, family history of premature CAD, history of coronary artery disease, history of MI, history of peripheral vascular disease, history of stroke/cerebrovascular event, smoking, socioeconomic status, education level, alcohol use, high sensitivity cardiac troponin levels, NT-proBNP levels,
estimated glomerular filtration rate, urine albumin to creatinine ratio, total cholesterol levels, LDL-c levels, HDL-c levels, ECG based left ventricular hypertrophy, and baseline therapies for diabetes (any therapy (yes vs. no), insulin use (yes vs. no)) and CV risk modification (statins (yes vs. no), anti-hypertensives (yes vs no))

**Defining pre-diabetes and T2DM Status:**

Pre-diabetes and T2DM will be diagnosed according to established criteria.(16) Participants will be classified as having T2DM if they have any of the following: 1) HbA1c ≥ 6.5%; or 2) fasting plasma glucose ≥ 126 mg/dL; or 3) use of antihyperglycemic medication. Participants who do not meet the criteria for T2DM will be classified as having pre-diabetes according to either of the following: 1) HbA1C 5.7 to 6.4%; or 2) fasting plasma glucose of 100 to 125 mg/dL. Participants who do not meet the criteria for either pre-diabetes or T2DM will be classified as having neither pre-diabetes or T2DM.

**Brief Analytic Plan:**

The primary analysis will be in patients with T2DM. The secondary analysis will include all patients with either pre-diabetes or T2DM. The study cohorts will be harmonized for the covariates of interest; continuous variables will be standardized to z scores to allow for comparability & categorical variables will be categorized uniformly across cohorts. For the development of the HF risk score, the pooled ARIC and CHS cohorts will used as the derivation cohort and the pooled DHS and MESA cohorts as the validation cohort.

**Risk score development (in the derivation cohort):**

- Among pooled participants from the ARIC and DHS, the univariable association between baseline characteristics listed above and risk of incident HF will be assessed using unadjusted Cox proportional hazards models.
- All candidate variables with less than 10% missing rate will be imputed to the median of the non-missing values for continuous variables or to the most frequently occurring group for categorical variables. Variables with more than 10% missing will be excluded from the analysis.
- Baseline characteristics with a significant univariable association with incident HF in unadjusted analyses will be tested in a common Cox proportional hazards (PH) model, which will then be used to estimate the independent association of each baseline characteristic with incident HF risk. Backward selection approach will be used a-priori with a retention p-value criterion of < 0.05 for the final multivariable model. Continuous variables will be tested for nonlinearity using generalized additive models as described previously and polynomial terms will be considered for non-linear covariates.(17)
- Established clinical thresholds for categorical handling of covariates, if available, will also be tested for relevant clinical predictors (NT-proBNP ≥ 100 ng/L; hs-cTnT ≥ 6 ng/L; LVH on ECG = present/absent; hsCRP > 3 mg/L; eGFR < 60 ml/min/1.73m²; and BMI ≥ 30 kg/m²). The full multivariable model will include all variables with an adjusted P-value of < 0.10 for retention. Shrinkage methods such as Lasso will be used to avoid overfitting.(17) More parsimonious models will also be evaluated to determine if simpler models perform adequately.
- Using the significant predictors of incident HF in the adjusted Cox PH model, we will develop a weighted point score to estimate the 10-year risk of incident HF. The integer score will consider both pre-specified dichotomous and ordinal clinical cut-points for continuous predictors: NT-proBNP ≥ 100 ng/L, hs-cTnT ≥ 6 ng/L, LVH on ECG = present, hsCRP > 3 mg/L, eGFR < 60 ml/min/1.73m², BMI ≥ 30 kg/m². The number of points added will be scaled according to the strength and direction of association noted in the analysis above. Calibration of the model will be evaluated by the Hosmer-Lemeshow statistic $\chi^2$.

**Evaluation of model performance and comparison vs. other HF risk scores**

- Discrimination and calibration of the developed model will be evaluated using Harell’s c-statistic and the Nam-D’Agostino $\chi^2$ goodness-of-fit test. The new models will be compared with the Health ABC score (an established model for HF prediction) using the C-statistic, the change in the area under the receiver operating curve for the new vs. the established models, the net reclassification index (NRI), the continuous NRI, and the integrated discrimination index (IDI).
Validation of the risk score (MESA & CHS pooled cohort):

- The discrimination and calibration of the risk score will also be tested in the pooled validation cohort of MESA and DHS participants. Calibration will be tested by plotting the observed HF risk versus predicted HF risk across quintiles of the HF risk score categories. The HF risk score calibration capability will be assessed both visually and using the Nam-D'Agostino $\chi^2$ goodness-of-fit test; a non-significant $\chi^2$ (p-value > 0.05) indicates good calibration.

Sensitivity analyses

- Sensitivity analyses will also be performed to determine the significant predictors of HF and develop a HF risk prediction score among patients with vs. without prevalent ASCVD at baseline separately.
- A risk prediction model will also be developed to predict the risk of incident HF or CV death using the strategy described above.

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 ___X_ 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 ___X_ 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.cscu.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)? Proposal reviewed on similar topic included: MP1197, MP1376, MP1808, MP1883, MP2775

These prior proposals have looked at risk of HF in relation to different exposures. We are planning to pool data from 4 large cohorts and use the same for developing a risk score for HF in patients with diabetes. This pooled analysis proposal is unique does not overlap with prior studies done in ARIC. We have also included Dr. Ballantyne, who has led many of the risk prediction for HF studies in ARIC, as a coauthor/primary ARIC investigator in our proposal.
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.