ARIC Manuscript Proposal #3545

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1.a. Full Title: Identification of Cardiovascular Disease Risk Equivalent among Patients with Diabetes Mellitus

b. Abbreviated Title (Length 26 characters): CVD risk equivalent among patients with diabetes

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

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3. Timeline:
Dec 2019-Jan 2020 proposal approval and data acquisition
Jan 2020-May 2020 data analysis/ abstract submission to AHA
May 2020-July 2020 manuscript writing
July 2020- Dec 2020 manuscript revising and submission

4. Rationale:

The concept of the “CHD risk equivalent” was first introduced by Haffner et al.[1] In this landmark study, the investigators observed that the myocardial infarction (MI) incidence rate for diabetic subjects without prior MI (DM+/MI-) was twice the rate as that among those without DM and MI (DM-/MI-) and as high as that of those who had a history of MI but no DM (DM-/MI+). These results demonstrated that diabetic patients a CHD risk comparable to the secondary prevention population and should be given similar approach to management.

Subsequent studies have addressed the question “Is DM a CHD risk equivalent?”. Although more recent studies have been inconsistent [2-6]. A meta-analysis of 13 cohort studies comprised of 45,108 participants showed that those with diabetes had 43% lower risk for future CAD events (fatal or non-fatal myocardial infarction) compared with those with a prior MI [5]. A recent study of 1.6 million Kaiser Permanente Northern California patients aged 30-90 years found those with DM but no history of CHD had a 39% lower 10-year CHD risk than those with CHD and no history of diabetes. The subgroup of DM patients with over 10 years of DM duration had comparable CHD risk to the CHD and no diabetes group [6]. Kuusisto et al. pointed out in their review that multiple reason could potentially contribute to the different conclusion [7]. For instance, compared to the studies with negative finding, the studies supporting DM as “CHD risk equivalent” tend to include more severe DM, or to be more Caucasian dominated, or to have longer follow-up time [2-4]. In addition, contemporary DM population is very different from the older one in aspects such as diagnosis algorithm, treatment strategies, comorbidity profiles and DM severity, all of which influence the varying answers to the question “is DM a CVD risk equivalent for global CVD events”.

We first aim at examining whether DM is a CVD risk equivalent in a large pooled, contemporary cohort from the US population. Given the DM population is a heterogenous risk entity, we would like to examine how the severity of DM, measured by DM duration, HbA1c control and insulin use, influences the CVD risk among DM compared to those with prior CVD but no DM when controlled for other risk factors.

The current 2018 AHA/ACC lipid management guidelines identify DM with 10-year ASCVD risk>=20% or with multiple risk factors as higher risk subgroup and recommend them high intensity statin instead of moderate statin. While this is an improvement of risk stratification among CVD-free DM compared to the “CHD risk equivalent” approach, such non-DM specific algorithm or “risk factor count” approach may not be accurate enough [8]. Besides, there could exist a “very high risk” subgroup among the primary prevention DM population with comparable CVD risk as those with both DM and prior CVD. This “very high risk” DM population, although without prior CVD, may benefit the same from maximal dose statin or combined therapy as the very high-risk CVD patients. We aim to identify subgroups of “high-risk” and “very-high risk” among CVD-free DM patients by using quantitative method to integrate the excessive risk caused by DM and other comorbidities. A better stratification of DM population will rationalize the needs to investigate the benefit of maximal dose preventive treatment.

5. Main Hypothesis/Study Questions:

Objectives

1. Compare the risk of future CVD among four risk groups defined by DM and prior CVD status (DM-/CVD-, DM+/CVD-, DM-/CVD+ and DM+/CVD+) in a pooled cohort of US population;
2. Further categorize DM+/CVD- group into subgroups by DM duration, or HbA1c control, or Insulin use and compare the risk of future CVD among the subgroups DM+/CVD- to that of the DM-/CVD+ group.
3. Identify a subgroup of "high-risk" CVD-free DM subjects with a comparable risk as those DM-/CVD+ and a subgroup of "very high-risk" CVD-free DM subjects with a comparable risk as those DM+/CVD+ and compare their characteristics (risk factors, medication and CVD risk) to those with DM but a lower risk and to those with CVD only;

Hypothesis

1. Compare to the DM-/CVD- group, there is stepwise increase of CVD risk in the DM+/CVD-, DM-/CVD+ and DM+/CVD+ groups;
2. DM with long duration, poor HbA1c control and insulin use will have higher CVD risk, closer to that in DM-/CVD+ group compared to those with less severe DM.
3. The subgroup of "very high risk" DM+/CVD- subjects with a comparable risk as those DM+CVD+ will have poorest risk profile and highest CVD risk among all with DM+/CVD-.

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).

Study sample

In this project we will pool four US cohorts on cardiovascular studies with diverse ethnical, geographical and temporal background: Atherosclerosis Risk In Communities (ARIC), Multi-Ethnic Study of Atherosclerosis (MESA), Jackson Heart Study (JHS) and Framingham Heart Study Offspring cohort (FHS offspring) [9-12]. Because HbA1c is one of the current DM diagnosis criteria, the project will use the exam in each cohort when HbA1c measure was available instead of the original baseline. We will include all subjects between ages of 30-84.

Participants will be classified into four groups: (DM-/CVD-, DM+/CVD-, DM-/CVD+ and DM+/CVD+). DM is defined as having at least one of the following before or at baseline: (1) Use of diabetes medication; (2) Self report of DM; (3) Fasting blood glucose of ≥6.99 mmol/l (126 mg/dl); (4) 2h post-challenge glucose ≥11.1 mmol/l (200 mg/dl); or (5) A HbA1c ≥6.5% (48 mmol/mol). Prevalent CVD at baseline is defined as having at least one of below before the baseline exam: (1) Prior myocardial infarction; (2) prior stroke; (3) prior HF; (4) prior PAD. The CVD-free DM group will be further classified in the following ways: (1) DM duration: undiagnosed DM newly found at baseline by glucose/HbA1c levels, diagnosed DM <5 years, 5-10 years and 10+ years; (2) HbA1c control: <7% vs.>=7%; (3) insulin use: yes vs. no.

Baseline Risk factors

1. Demographic and behavioral risk factors: age, sex, race/ethnicity, family history of premature CVD, smoking status; alcohol use
2. clinical measures: body mass index, systolic blood pressure (SBP) and diastolic blood pressure (DBP);

3. DM-specific measures: diabetes duration, hemoglobin A1c (HbA1c), insulin use, oral hypoglycemic medication;
4. Lab tests: high sensitivity C-reactive protein, high-density lipoprotein-cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), triglycerides, total cholesterol.
5. Comorbidities: atrial fibrillation,estimated glomerular filtration rate (eGFR), use of lipid-lowering medication, anti-hypertensive treatment, anti-platelet medication;

Follow-up and Endpoint Definitions

Primary endpoint of interest is incident CVD, a composite endpoint including myocardial infarction, coronary heart disease death, fatal and non-fatal stroke, heart failure and CVD death. Time to event is recorded as the time from baseline exam to any of above event happening earliest after baseline. Secondary endpoint is CHD which includes myocardial infarction and coronary heart disease death. The adjudication process for events involved a panel to review hospitalization and death data per study protocols previously published [9-12]. According to the designated baseline exam in the project, maximum follow-up time in years will be approximately 25 years for ARIC, 12 years for MESA, 15 years for JHS and 17 years for FHS Offspring cohort.

Statistical analysis

1. Descriptive analysis of all risk factors among DM-/CVD-, DM+/CVD-, DM-/CVD+ and DM+/CVD+ groups: All continuous variables will be compared among groups using ANOVA. Continuous variable with skewness >1 will be log transformed to get normal distribution. The chi-square test will be used to compare categorical variables.
2. CVD and CHD event rate per 1000 person-years will be calculated in above four groups, crude and standardized to total sample age, gender and race; event rates will also be calculated according to the subgroups (duration, HbA1c control, insulin use) in DM+/CVD- group;
3. Cox proportional hazard regression model will be used to calculate the HR of CVD and CHD risk for DM+/CVD-, DM-/CVD+ (overall and by duration, HbA1c control, insulin use) and DM+/CVD+ groups vs. DM-/CVD- group when:
   - Unadjusted;
   - Adjusted for age, gender and race;
   - Adjusted for all risk factors;

4. Examine risk factors that modify the hazard ratio between DM+/CVD- (overall and by duration, HbA1c control, or insulin use) and DM-/CVD+ groups:

In the Cox regression model, examine interaction between DM/CVD groups and age, gender, race (white vs. non-white), cohorts (ARIC vs. other cohorts), family history of CVD (Yes/No), current smoking (Yes/No), hypertension (Yes/No), LDL-C dyslipidemia (LDL-C < 100mg/dl vs. ≥ 100mg/dl), HDL-C dyslipidemia (HDL-C < 40mg/dl for men or < 50mg/dl for women), obesity (BMI < 30 kg/m^2 vs. ≥ 30 kg/m^2), microalbuminuria (Yes/No), Chronic kidney Disease (Yes/No) and atrial fibrillation (Yes/No), statin use (Yes/No) and anti-platelet medication (Yes/No), adjusted for all risk factors with a p value <0.15 (we intend to set a loose p value limit to include maximal potential significant risk factors). Interaction between DM/CVD groups and continuous variables involved in above categorical variables will also been examined (SBP, DBP, LDL-C, HDL-C, BMI, and eGFR). For the categorical

variable(s) with significant interaction with DM/CVD variables ($p<0.1$ for interaction) we will repeat the cox regression model within each subgroup of that categorical variable.

5. Define the "high-risk" and "very high-risk " in the DM+/CVD- group:
   - In the Cox regression model, include DM/CVD categories as 4 dummy variables, as well as other significant risk factors and interaction (dummy variable called DM-/CVD- will be leave out of model as reference group);
   - Beta coefficients are defined as β_1 for DM+/CVD- variable, β_2 for DM-/CVD+ variable, β_3 for DM-/CVD+ variable,β_z for main term of other variables and β_{1z} for interaction of DM-/CVD+ variable and other variables in the model;
   - For anyone from the DM+/CVD- group with a comparable risk to the average risk of the DM-/CVD+ group, his/her risk factor value Z will satisfy the equation:

$$1 - S_t^{e^{(\beta 1 * 1 + \sum \beta z * Z + \sum \beta 1z * Z)}} = 1 - S_t^{e^{(\beta 2 * 1 + \sum \beta 2z * Z)}}$$

   So we get :

$$\beta_1*1 + \sum\beta_z*Z + \sum\beta_{1z}*Z = \beta_2*1 + \sum\beta_{2z}*Z$$

   - Similarly, for anyone from the DM+/CVD- group with a comparable risk to the average risk of the DM+/CVD+ group, his/her risk factor value Z will satisfy the equation, $\beta_1*1 + \sum\beta_z*Z + \sum\beta_{1z}*Z = \beta_3*1 + \sum\beta_{3z}*Z$
   - Categorize the DM+/CVD- group into three subgroups as:

1) "lower risk" when $\beta_1*1 + \sum\beta_z*Z + \sum\beta_{1z}*Z < \beta_2*1 + \sum\beta_{2z}*Z$
2) "high risk" when $\beta_2*1 + \sum\beta_{2z}*Z <= \beta_1*1 + \sum\beta_z*Z + \sum\beta_{1z}*Z < \beta_3*1 + \sum\beta_{3z}*Z$
3) "very high risk" when $\beta_1*1 + \sum\beta_z*Z + \sum\beta_{1z}*Z >= \beta_3*1 + \sum\beta_{3z}*Z$

6. Compare the risk factor profile and incident CVD risk among the above three risk categories in subjects with DM.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes _X_ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ____ Yes ____ No
(The 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 current derived consent file ICTDER05 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)?

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 https://sites.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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